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

Study Intervention Number:	PF-07252220
Study Intervention Name:	Influenza modRNA Vaccine
US IND Number:	27600
EudraCT Number:	N/A
ClinicalTrials.gov ID:	NCT05540522
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4781004
Phase:	3

Brief Title: A Study to Evaluate the Efficacy, Safety, Tolerability, and Immunogenicity of a Modified RNA Vaccine Against Influenza in Adults 18 Years of Age or Older

Document History

Document	Version Date
Amendment 4	27 June 2023
Amendment 3	26 March 2023
Amendment 2	09 November 2022
Amendment 1	28 July 2022
Original protocol	07 June 2022

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

Protocol Amendment Summary of Changes Table

Amendment 4 (27 June 2023)

Overall Rationale for the Amendment:

In response to regulatory agency feedback, moved immunogenicity to a secondary endpoint (from exploratory) and included the use of HAIs CCI [redacted] to quantify immune responses.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
1.1 Synopsis	Updated to reflect the equivalent revisions in the body of the protocol.	To ensure the language is consistent with the body of the protocol.	Substantial.
2.2.3 Nucleoside-Modified mRNA Vaccines	• Changed the number of BNT162b2 doses administered to the number of BNT162b2 doses that have been distributed. • Updated the incidence of myocarditis after COVID-19.	To align with the emerging data and established safety profile of the COVID-19 vaccine.	Substantial.
2.2.5 Clinical Overview	Abbreviated the results from the Phase 1/2 study (C4781001) and stated that the preliminary results can be found in the IB.	Additional guidance to the investigator relating to where the latest influenza vaccine immunogenicity results can be found.	Substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
2.3 Benefit/Risk Assessment	Added a statement that over 19,000 adults have received qIRV in ongoing clinical trials and no safety concerns have been observed to date.	For clarity.	Substantial.
3 Objectives, Endpoints, and Estimands	• Updated the approach for analysis of safety data by age stratum (local reactions and systemic events analyzed separately, AEs and SAEs analyzed separately and combined). • 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]	Revisions to the immunogenicity objectives are to align with regulatory agency feedback and the agency's requirement to use an CCI [redacted] HAI as the primary means of evaluating the immune responses when using CCI [redacted] vaccine comparator.	Substantial.
4.1 Overall Design	Revised the number of southern hemisphere participants from up to approximately CCI [redacted] to up to approximately CCI [redacted], and updated the total number of participants to reflect this.	To align with regulatory documentation.	Substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
4.3 Justification for Dose	Updated to reflect the latest qIRV dose justification based on results from the Phase 1/2 study (C4781001).	Additional context for dose justification.	Substantial.
8.2.2 Immunogenicity Assessments	Updated to reflect the use of HAIs CCI [redacted] to quantify immune responses, and to specify that not all samples will be tested using both HAIs at every visit.	To reflect the corresponding revisions to the Objectives, Endpoints, and Estimands section.	Substantial.
9.1.2 Immunogenicity	Added details of the hypothesis testing for the secondary immunogenicity objective evaluating the noninferiority of the immune response to qIRV compared to QIV for each age stratum.	To reflect the corresponding revisions to the Objectives, Endpoints, and Estimands section.	Substantial.
9.1.3.2 Secondary Estimands	Provided details of the secondary estimands associated with the secondary immunogenicity objectives.	To reflect the corresponding revisions to the Objectives, Endpoints, and Estimands section.	Substantial.
9.1.4 Multiplicity Adjustment	Updated to reflect the hypothesis testing for the amended secondary immunogenicity objectives and the hierarchical manner in which the hypothesis testing related to these objectives will occur.	To reflect the corresponding revisions to the Objectives, Endpoints, and Estimands section.	Substantial.
9.2 Analysis Sets	Added additional evaluable populations to align with the additional immunogenicity objectives.	To reflect the corresponding revisions to the Objectives, Endpoints, and Estimands section.	Substantial.
9.3.2 Primary Endpoint(s)/Estimand(s) Analysis	Updated to reflect the amended safety objective and related analyses.	To reflect the corresponding revisions to the Objectives, Endpoints, and Estimands section.	Substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis	Updated to reflect the secondary immunogenicity objectives and related analyses.	To reflect the corresponding revisions to the Objectives, Endpoints, and Estimands section.	Substantial.
9.3.4 Tertiary/Exploratory Endpoint(s) Analysis	Updated the tertiary/exploratory objectives and related analyses.	To reflect the corresponding revisions to the Objectives, Endpoints, and Estimands section.	Substantial.
9.6.2 Immunogenicity	Added details of the immunogenicity sample sizes for samples CCI [redacted] (that will be used for the noninferiority assessment of qIRV compared to QIV).	For clarity.	Substantial.
10.10 Appendix 10: Protocol Amendment History	Relocated to the SoC table (from the previous amendment) to the appropriate appendix.	Version control.	Nonsubstantial.

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

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

Brief Title:

A Study to Evaluate the Efficacy, Safety, Tolerability, and Immunogenicity of a Modified RNA Vaccine Against Influenza in Adults 18 Years of Age or Older

Regulatory Agency Identification Number(s):

US IND Number:	27600
EudraCT Number:	N/A
ClinicalTrials.gov ID:	NCT05540522
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4781004
Phase:	3

Rationale:

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

Over the last several years, the use of mRNA as the basis for potential vaccine candidates has shown increasing promise. Various approaches to optimize the response to mRNA vaccines have been used. This includes modRNA in which some nucleosides are replaced by naturally occurring modified nucleosides, such as pseudouridine, which decreases innate immune activation and increases translation. Two LNP-encapsulated modRNA vaccines encoding the SARS-CoV-2 spike protein have been developed in response to the public health emergency presented by the COVID-19 pandemic: BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), with both vaccines demonstrating high effectiveness with no significant safety concerns during Phase 3 development. Since its first marketing authorization in December 2020, over 4 billion doses of BNT162b2 have been distributed worldwide. Postauthorization safety surveillance has confirmed the safety profile observed in clinical trials and has also identified adverse reactions of anaphylaxis (estimated at 11.1 per million doses administered) and an increased risk of myocarditis and pericarditis. Myocarditis was reported more often

after the second COVID-19 vaccination and the risk was highest in younger males. Despite differences in the source of the data, design of the reported studies, geographic region, or method of ascertainment, the postmarketing safety surveillance and observational studies converge to a very rare frequency of myocarditis after COVID-19 vaccination, ie, less than 1 extra case per 10,000 vaccinees (<0.01%).

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

A Phase 1/2 study (C4781001) to describe the safety, tolerability, and immunogenicity of a modRNA vaccine against influenza in healthy individuals was initiated in September 2021 in participants 65 through 85 years of age. This study is being conducted across 2 substudies – Substudy A and Substudy B – to study different modRNA vaccine schedules against influenza. Based on 28-day safety and immunogenicity data from this study, 1 dose of qIRV encoding 2 A strains and 2 B strains has been selected for study in Phase 3. Based on Phase 2 safety and immunogenicity data, the dose level of qIRV by age stratum is CCIµg for participants 18 through 64 years of age and CCIµg for participants ≥65 years of age. The latest results can be found in the IB for qIRV.

This is a Phase 3, randomized, observer-blinded study to evaluate the efficacy, safety, tolerability, and immunogenicity of a single dose of qIRV against influenza compared to licensed inactivated influenza vaccine in healthy adults 18 years of age and older (stratified by age: 18 through 64 and ≥65 years of age).

Objectives, Endpoints, and Estimands:

Please see the table below for the definitions of LCI, CCI, ILI, and severe LCI.

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 Systemic symptoms: • CCI
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 >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 ≥38.0°C (≥100.4°F)
LCI	Influenza infection confirmed through RT-PCR or culture at the central laboratory, unless otherwise specified

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

Abbreviations: CCI = culture-confirmed influenza; HAI = hemagglutination inhibition assay; ILI = influenza-like illness; LCI = laboratory-confirmed influenza; RT-PCR = reverse transcription–polymerase chain reaction.

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.

The study objectives, endpoints, and estimands are detailed below.

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

Objectives	Estimands	Endpoints
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 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 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
	• 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 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 RT-PCR, 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 RT-PCR, 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 HAIs CCI [redacted])	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 HAIs CCI [redacted] for the influenza strains that are present in the study interventions: • 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 [redacted] 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 HAIs 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 HAIs CCI for the influenza strains that are present in the study interventions: • 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 HAIs 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		

Objectives	Estimands	Endpoints
CCI		

Objectives	Estimands	Endpoints
CCI [redacted]		

There are no primary immunogenicity objectives in this study.

For the purposes of the study estimands:

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

Overall 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 initially 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 proceed only if regulatory authority endorsement is obtained to do so. Enrollment into each of the 2 age strata (18 through 64 and ≥65 years of age) may therefore occur independently. Based on Phase 2 safety and immunogenicity data, the dose level of qIRV by age stratum is CCI µg for participants 18 through 64 years of age and CCI µg for participants ≥65 years of age.
- 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. 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. An additional optional blood sample of 50 mL may be collected from participants who consent to the time points specified in Section 1.3 for assessment of CCI; the number of participants asked to provide these samples will be determined by Pfizer, contingent on operational considerations.
  - 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.

Up to approximately CCI additional participants may be enrolled during the second season and randomized CCI to receive 1 dose of either qIRV or seasonal QIV comparator. Of these additional participants:

- The number of participants 18 through 64 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 at 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. CCI [redacted] Within each age stratum, hypothesis testing relating to the VE and immunogenicity objectives will occur in a hierarchical manner as described in the protocol.

If the primary efficacy analysis for qIRV is not favorable, at the sponsor's discretion, the study may be unblinded early and, if still during the influenza season, participants who were randomized to receive qIRV may be offered a licensed QIV.

Following vaccination, for all participants, AEs will be collected from informed consent signing through 4 weeks following vaccination, and SAEs will be collected from informed consent signing through 6 months after vaccination. In addition, AEs occurring up to 48 hours after blood draws or collection of midturbinate swabs will be collected. Deaths, pneumonia, and hospitalizations related to ILIs will be recorded for the entire study duration.

Number of Participants:

Up to approximately 53,200 participants may be enrolled in the study.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization.

Study Population:

Inclusion Criteria

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

Age and Sex:

1. Male or female participants ≥18 years of age (or the minimum age of consent in accordance with local regulations) at Visit 1 (Day 1).

    - Refer to Appendix 3 for reproductive criteria for male (Section 10.3.1) and female (Section 10.3.2) participants.

Disease Characteristics:

- Not applicable.

Other Inclusion Criteria:

2. Participants who are willing and able to comply with all scheduled visits, investigational plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

    Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.9.

4. Capable of giving signed informed consent as described in the protocol, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Exclusion Criteria

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

Medical Conditions:

1. Medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality, that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. History of severe adverse reaction associated with any vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

3. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

   Note: Individuals who have had a splenectomy or have functional asplenia will be considered ineligible.

4. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

5. Allergy to egg proteins (egg or egg products) or chicken proteins.

Prior/Concomitant Therapy:

6. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

7. Receipt of blood/plasma products or immunoglobulin from 60 days before study intervention administration, or planned receipt throughout the study.

8. Vaccination with any investigational or licensed influenza vaccine within 6 months (175 days) before study intervention administration, or ongoing receipt of chronic antiviral therapy with activity against influenza.

9. Any participant who has received or plans to receive a modRNA-platform SARS-CoV-2 vaccine within 14 days before or after study vaccination at Visit 1.

Prior/Concurrent Clinical Study Experience:

10. Participation in other studies involving administration of a study intervention within 28 days prior to, and/or during, participation in this study.

    Note: In addition to administration of investigational products, study interventions may include additional procedures, such as collection of biological samples. Therefore, participants may not be in another study whereby procedures, such as respiratory illness visits, may interfere with compliance with this study's protocol.

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

11. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

Study Arms and Duration:

A participant is considered to have completed the study either when they have completed the last visit (Visit 4; 6-month follow-up visit) or when the influenza season ends (as judged by Pfizer based on epidemiological data), whichever occurs later.

Study Interventions		
Intervention Name	**qIRV**	**QIV**
Type	Vaccine	Vaccine
Targeted influenza strains	For each season - strains as recommended by WHO for influenza vaccines.	For each season - strains as recommended by WHO for influenza vaccines.
Unit dose strength(s)	Based on Phase 2 safety and immunogenicity data, the dose level of qIRV by age stratum is CCI µg for participants 18 through 64 years of age and CCI µg for participants ≥65 years of age.	As detailed in the IPM.
Route of administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Comparator
IMP or NIMP (global designation)	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor or locally by the trial site (local sourcing by the trial site is not permitted without sponsor approval)

Study Interventions		
Intervention Name	**qIRV**	**QIV**
Packaging and labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided as either a PFS or a glass vial as open-label supply. Each dispensable unit will be labeled per country requirement.

If the primary efficacy analysis is not favorable, at the sponsor's discretion, the study may be unblinded early and, if still during the influenza season, participants who were randomized to receive qIRV may be offered a licensed QIV. This QIV will be considered NIMP, sourced locally by site and administered per the local package insert.

Statistical Methods

The planned sample size for the study is based on statistical hypothesis testing for RVE of qIRV compared to seasonal QIV in each age stratum (18 through 64 and ≥65 years of age).

The study objectives for each age stratum will be assessed separately without multiplicity adjustment.

There are 2 hypotheses (noninferiority and superiority) for the study primary efficacy objectives in each stratum, which will be tested in hierarchical order. The hypothesis of superiority of VE will be tested only if the null hypotheses for noninferiority of VE is rejected. The hypotheses for the study secondary immunogenicity objectives for each age stratum will be tested after the primary efficacy objectives in that age stratum have been met.

The study primary noninferiority efficacy objective for each age stratum is achieved if the lower bound of the 95% CI for RVE is more than CCI.

The study primary superiority efficacy objective for each age stratum is achieved if the lower bound of the 95% CI for RVE is more than CC.

Noninferiority of the immune response elicited by qIRV compared to a seasonal QIV will be evaluated using HAI titers against seasonal strains recommended by WHO for the 2022-2023 northern hemisphere influenza season.

All RVEs will be estimated using the exact conditional binomial method. The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each vaccine group. A 3-tier approach will be used to summarize AEs.

There is no planned interim analysis for the study.

Ethical Considerations:

Potential risks to individual participants may include the following, mitigations for which are detailed in the protocol:

- Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination. These are common adverse reactions seen with other vaccines, as well as the COVID-19 vaccine BNT162b2, which is also based on modRNA. Local and systemic reactions to QIV may occur.

- The safety profile of a novel vaccine is not yet fully characterized, so the full extent of risks is unknown.

- Cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.

- Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic. Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.

- Venipuncture will be performed during the study. There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.

- Midturbinate swabs will be collected by site staff at any in-person ILI visit. Midturbinate swabs will be self-collected by the participant at any ILI visit conducted as a telehealth visit. There is a risk of nasal bleeding or injury.

Benefits to individual participants may be:

- Receipt of a potentially efficacious influenza vaccine at no cost to the participant, and provision of the immunogenicity results in a subset of participants.

- Active surveillance for and access to evaluation of respiratory illnesses.

- Contributing to research to help others.

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

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Visit Number	1	2	3	4	Unplanned
Visit Description	**Vaccination**	**1-Week Follow-Up Visit[a,b]**	**4-Week Follow-Up Visit[b]**	**6-Month Follow-Up Visit[b]**	**ILI Visit[c]**
Visit Window (Days)	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Within 5 Days After ILI Onset**
Visit Type/Location	**Site**	**Site or Home Health**	**Site or Home Health**	**Site, Telehealth, or Home Health**	**Site, Telehealth, or Home Health**
Obtain informed consent	X				
Assign participant number	X				
Obtain demography and medical history data	X				
Perform clinical assessment[d]	X				
Measure height and weight	X				
Measure oral temperature	X				
Collect prior COVID-19 and pneumococcal vaccine information	X				
Collect prior influenza vaccine information, if received within the 12 months prior to enrollment	X				
Collect nonstudy vaccine information	X	X	X	X	X
Collect prohibited medication use		X	X	X	X
Perform urine pregnancy test on WOCBP	X				
Confirm use of contraceptives (if appropriate)	X	X	X		X
Confirm eligibility	X				
Review temporary delay criteria	X				
Obtain randomization number and study intervention allocation	X				

Visit Number	1	2	3	4	Unplanned
Visit Description	**Vaccination**	**1-Week Follow-Up Visit[a,b]**	**4-Week Follow-Up Visit[b]**	**6-Month Follow-Up Visit[b]**	**ILI Visit[c]**
Visit Window (Days)	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Within 5 Days After ILI Onset**
Visit Type/Location	**Site**	**Site or Home Health**	**Site or Home Health**	**Site, Telehealth, or Home Health**	**Site, Telehealth, or Home Health**
Collect blood sample for immunogenicity assessment from participants in the immunogenicity subset[e]	~15 mL or ~50 mL		~15 mL or ~50 mL	~15 mL or ~50 mL	
Collect optional blood sample for [redacted] from participants who consent to this[f]	~50 mL	~50 mL	~50 mL	~50 mL	
Administer study intervention	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X				
Provide self-swab kits and instructions on self-collection of midturbinate swabs[g]	X				X
Obtain 2 midturbinate swabs (site-collected or self-swab), 1 from each nostril					X
Explain participant communication methods (including for reactogenicity e-diary completion for participants in the reactogenicity subset), assist the participant with downloading the app, or issue provisioned device, if required	X				
Provide/ensure the participant has a thermometer and measuring device	X				
Review reactogenicity e-diary data (daily review is optimal during the active reactogenicity diary period [Days 1 through 7])[h]	←	→			
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[h]		X	X		
Provide the participant with an ILI memory aid	X				
Collect ILI-related clinical and laboratory information					X
Collect AEs and SAEs as appropriate[i]	X	X	X	X	X
Perform clinical assessment, including oral temperature and respiratory rate[j]					X

Visit Number	1	2	3	4	Unplanned
Visit Description	**Vaccination**	**1-Week Follow-Up Visit[a,b]**	**4-Week Follow-Up Visit[b]**	**6-Month Follow-Up Visit[b]**	**ILI Visit[c]**
Visit Window (Days)	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Within 5 Days After ILI Onset**
Visit Type/Location	**Site**	**Site or Home Health**	**Site or Home Health**	**Site, Telehealth, or Home Health**	**Site, Telehealth, or Home Health**
Following ILI resolution, collect participant-reported outcome information[k]					X
Collect e-diary or assist the participant with deleting application[l]				X	

Abbreviations: COVID-19 = coronavirus disease 2019: CRF = case report form; ILI = influenza-like illness; WOCBP = women of childbearing potential.

a. Visit 2 will only be conducted for participants who have consented to provide the optional blood sample for CCI [redacted].
b. Visit may be completed as a home health visit (see Section 8.1.2). For participants not included in the immunogenicity subset, Visit 4 may be conducted as a telehealth visit (see Section 8.1.1).
c. The ILI visit may be conducted as an in-person (at the site or the participant's home), a home health, or a telehealth visit.
d. Including, if indicated, a physical examination.
e. Blood samples of approximately 15 mL will be collected for immunogenicity assessments. Approximately CC participants will be asked to consent to alternatively providing 50-mL blood samples at the same time points, which will be used for immunogenicity assessments and assay development.
f. An additional optional 50-mL blood sample will be collected for CCI [redacted] from participants who consent to this.
g. Participants will be provided with self-swab kits at Visit 1. Additional self-swab kits will be provided at subsequent visits if required (ie, if used or lost).
h. For participants in the reactogenicity subset only.
i. AEs are collected from the completion of informed consent to Visit 3. SAEs are collected from the completion of informed consent to Visit 4 (approximately 6 months after vaccination). Additionally, any AEs occurring up to 48 hours after a blood draw or collection of midturbinate swabs must be recorded.
j. Respiratory rate is assessed at in-person ILI visits only.
k. As detailed in Section 8.10.6.1.
l. If directed by Pfizer (eg, at the end of the influenza season).

2. INTRODUCTION

2.1. Study Rationale

This is a Phase 3, randomized, observer-blinded study to evaluate the efficacy, safety, tolerability, and immunogenicity of a single dose of qIRV against influenza compared to licensed inactivated influenza vaccine in healthy adults 18 years of age and older.

2.2. Background

2.2.1. Influenza

Influenza is a major cause of morbidity and mortality worldwide, occurring in annual seasonal epidemics and occasionally in global pandemics.[1] Symptomatic influenza infection causes a febrile illness with respiratory and systemic symptoms,[2] although it may often be asymptomatic.[3] The risk of complications and hospitalization from influenza is higher in people ≥65 years of age, young children, and people with certain underlying medical conditions. In the US, an average of >200,000 hospitalizations per year are related to influenza,[4] while the annual global number of deaths is estimated to range from almost 300,000 to over 600,000.[5] The burden of disease is significant among 18- through 64-year-olds; in the US, the estimated flu disease burden for the 2019-2020 season was 380,209 hospitalizations, with 160,888 accounted for by those 18 through 64 years of age.[6] The same data estimated that the US annual mortality burden among all ages was 20,342 deaths, with 7911 occurring among 18- through 64-year-olds.[6] Vaccination coverage for influenza among adults ≥18 years of age was 48.4% during that season.[7]

Influenza viruses are part of the *Orthomyxoviridae* family and are divided into 3 genera or types (A, B, and C) based upon antigenic differences in the nucleoprotein and matrix protein. Influenza A viruses are further classified into subtypes based upon the membrane glycoproteins, HA and NA.[8] The RNA genome is segmented, which allows genetic reassortment among viruses of the same type.[8] This genetic instability can result in the phenomenon known as antigenic shift, involving a major change in 1 or both of the HAs and NAs, which, if efficiently transmissible, can result in a pandemic. More common are multiple point mutations in the genome, leading to more minor changes in the HA and NA, known as antigenic drift.[4] This genetic instability is what necessitates vaccines that are tailored annually.[4]

2.2.2. Influenza Vaccination

The first influenza vaccines were licensed in the 1940s,[9] and now a number of different types of vaccine exist: inactivated, recombinant, and LAIV.[10] The viruses that form the basis for inactivated vaccines are replicated in either embryonated hens' eggs or mammalian cell lines,[11] and some are combined with an adjuvant, such as MF59, to improve the immune response, particularly important in older individuals.[10] Multivalent vaccines are produced for routine seasonal immunization, targeting 3 or 4 influenza viruses.[10] Trivalent vaccines target 2 A subtypes and 1 B virus, although these have been replaced by quadrivalent vaccines, which target an additional B virus (to cover 2 antigenically distinct lineages).[12] Standard

inactivated vaccines generally contain 15 µg of each HA for adult intramuscular injection, although the high-dose inactivated vaccine contains 60 µg of each HA.[13]

Because of the ongoing variability in circulating influenza viruses, recommendations for the viruses to be targeted by each influenza season's vaccines reflect the global influenza virus surveillance that continues throughout the year in both hemispheres.[13] This means that the schedule for vaccine production, release, and administration is highly compressed.

2.2.2.1. Assessing Influenza Vaccine Immunogenicity

Dependent upon the components included in each influenza vaccine, vaccination is intended to induce antibodies against HA and/or NA.[14] Strain-specific immunogenicity can be measured by the HAI and [redacted] assays, although antibody titers measured by the HAI are most commonly used to assess vaccine responses.[13] In general, an HAI titer between 1:32 and 1:40 is considered protective at a group level.[13] This is reflected in regulatory guidance, where, for example:

Seroconversion is defined as a prevaccination HAI titer <1:10 and a postvaccination HAI titer ≥1:40 or a prevaccination HAI titer ≥1:10 and a minimum 4-fold rise in postvaccination HAI antibody titer.[13]

A reasonable statistical correlate for an efficacy of 50% to 70% against clinical symptoms of influenza is defined as an HAI titer of 1:40.[15]

Regulatory guidance allows for authorization of a new seasonal influenza vaccine on the basis of immunogenicity and/or efficacy data.[15,16]

2.2.3. Nucleoside-Modified mRNA Vaccines

Over the last several years, the use of mRNA as the basis for potential vaccine candidates has shown increasing promise.[17] Various approaches to optimize the response to mRNA vaccines have been used. This includes modRNA, in which some nucleosides are replaced by naturally occurring modified nucleosides, such as pseudouridine, which decrease innate immune activation and increase translation.[17]

Two LNP-encapsulated modRNA vaccines encoding the SARS-CoV-2 spike protein have been developed in response to the public health emergency presented by the COVID-19 pandemic: BNT162b2 (Pfizer/BioNTech)[18] and mRNA-1273 (Moderna).[19] ModRNA vaccine candidate dose levels up to 100 µg[20] and 250 µg[19] were studied in the candidate-selection/dose-finding stage of development for the 2 vaccines, respectively. Phase 3 development was conducted with 2 doses of BNT162b2 30 µg[18] and 2 doses of mRNA-1273 100 µg,[21] with both vaccines demonstrated to be highly effective with no identified significant safety concerns.[18,21] Since its first marketing authorization in December 2020, over 4 billion doses of BNT162b2 have been distributed worldwide. Postauthorization safety surveillance has confirmed the safety profile observed in clinical trials and has also identified adverse reactions of anaphylaxis (estimated at 11.1 per million doses administered) and an increased risk of myocarditis and pericarditis. Myocarditis was

reported more often after the second COVID-19 vaccination and the risk was highest in younger males. Despite differences in the source of the data, design of the reported studies, geographic region, or method of ascertainment, the postmarketing safety surveillance and observational studies converge to a very rare frequency of myocarditis after COVID-19 vaccination, ie, less than 1 extra case per 10,000 vaccines (<0.01%).[22,23,24]

2.2.4. Potential for mRNA Influenza Vaccines

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

The modRNA platform would present a number of potential advantages. Manufacturing could be accelerated as no reassortant step is required to produce manufacturing strains. This allows the decision on HA sequence to be made later than with current vaccines, and no egg adaptation is required, reducing the probability of vaccine being mismatched with circulating strains. The induction of not only anti-HA antibodies but also potential CD4+ and CD8+ T-cell responses (as seen with BNT162b2)[25] could improve upon the efficacy observed with existing influenza vaccines.

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

2.2.5. Clinical Overview

A Phase 1/2 study (C4781001) to describe the safety, tolerability, and immunogenicity of a modRNA vaccine against influenza in healthy individuals was initiated in September 2021, initially in participants 65 through 85 years of age. This study was conducted across 2 substudies – Substudy A and Substudy B. Substudy A described the safety and immunogenicity of mIRV A or B at 4 dose levels, bIRV encoding both A and B strains in 4 dose-level combinations, and qIRV encoding 2 A strains and 2 B strains at a dose level of CCI µg per strain. Additionally, Substudy A described:

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

Substudy B described the safety and immunogenicity of the following vaccination schedules in participants 65 through 85 years of age:

- 2 Doses of qIRV encoding 2 A strains and 2 B strains at a dose level of CCI µg per strain, administered 21 days apart.
- 2 Doses of licensed QIV, administered 21 days apart (as a control group).

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

Additionally, participants 18 through 64 years of age were included in Substudy B only during expanded enrollment: 240 participants 18 through 64 years of age were randomized [redacted] to receive either a single [redacted] µg dose of qIRV (encoding 2 A strains and 2 B strains at a dose level of [redacted] µg per strain) or a single [redacted] µg dose of qIRV (encoding 2 A strains and 2 B strains at a dose level of [redacted] µg per strain).

At the time of protocol amendment 4 for this study (C4781004), the final CSR is pending for the C4781001 study, but preliminary results can be found in the IB. Based on these safety and immunogenicity data from Study C4781001, 1 dose of qIRV encoding 2 A strains and 2 B strains has been selected for study in Phase 3. Based on Phase 2 safety and immunogenicity data, the dose level of qIRV by age stratum is [redacted] µg for participants 18 through 64 years of age and [redacted] µg for participants ≥65 years of age.

2.3. Benefit/Risk Assessment

modRNA vaccines expressing the SARS-CoV-2 spike protein have been shown to be safe, adequately tolerated, and efficacious in the prevention of COVID-19 when administered as 2 doses at a 21- to 28-day interval.[18,21] These vaccines have been authorized in many countries around the world, and since its first marketing authorization in December 2020, over 4 billion doses of BNT162b2 have been distributed worldwide.

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

To date, approximately 19,000 participants have been vaccinated with a qIRV modRNA influenza vaccine across a Phase 1/2 study (C4781001) and this Phase 3 study (C4781004). No safety concerns have been observed to date.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of qIRV may be found in the IB, which is the SRSD for this study. The SRSD for QIV is the Fluzone Quadrivalent USPI.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): qIRV		
Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines,[26] as well as the COVID-19 vaccine BNT162b2, which is also based on modRNA. The most common events reported in a large-scale efficacy study with BNT162b2 (C4591001) were mild to moderate pain at the injection site, fatigue, and headache.[18] 1-Week follow-up reactogenicity data of 194 participants who received mIRV, bIRV, or qIRV in C4781001 Substudy A and 120 participants from C4781001 Substudy B showed most events to be mild to moderate in severity, with the most common events being pain at the injection site, fatigue, and headache.	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol. All study participants will be observed for at least 30 minutes after vaccination.
The safety profile of a novel vaccine is not yet fully characterized.	Although qIRVs are novel vaccines, they are based on the same platform (modRNA) as the COVID-19 vaccine BNT162b2, which has been shown to have a positive benefit/risk profile.	AE and SAE reports will be collected from the signing of the ICD through 4 weeks and 6 months after the vaccination, respectively. All participants will be observed for at least 30 minutes after vaccination.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.	Anaphylaxis: The estimated rate is 5.0 per million doses administered.[27] Myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine, within several days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.	Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. Receipt of any mRNA-platform SARS-CoV-2 vaccine within 14 days before and 14 days after study vaccination is prohibited. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.10.8.
Study Intervention: QIV		
Local and systemic reactions to the vaccine may occur.	The following summary represents an example QIV safety profile: In adults 18 years of age and older, the most common (≥10%) injection-site reaction was pain (47%); the most common solicited systemic adverse reactions were myalgia (24%), headache (16%), and malaise (11%). In adults 65 years of age and older, the most common (≥10%) injection site reaction was pain (33%); the most common solicited systemic adverse reactions were myalgia (18%), headache (13%), and malaise (11%).[28]	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol. All study participants will be observed for at least 30 minutes after vaccination.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure appropriate COVID-19 prevention strategies.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.
Midturbinate swabs will be collected by site staff at any in-person ILI visit. Midturbinate swabs will be self-collected by the participant at any ILI visit conducted as a telehealth visit.	There is a risk of nasal bleeding or injury.	Only appropriately qualified personnel will collect the midturbinate swabs at site visits. Participants will be properly trained by site staff on self-collection of midturbinate swabs, in case the ILI visit is conducted as a telehealth visit.

2.3.2. Benefit Assessment

Benefits to individual participants may be:

- Receipt of a potentially efficacious influenza vaccine at no cost to the participant, and provision of the immunogenicity results in a subset of participants.
- Active surveillance for and access to evaluation of respiratory illnesses.
- Contributing to research to help others.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with qIRV are justified by the anticipated benefits that may be afforded to participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Please see Table 1 for the definitions of LCI, CCI, ILI, and severe LCI.

Table 1. 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 >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 ≥38.0°C (≥100.4°F)
LCI	Influenza infection confirmed through RT-PCR or culture at the central laboratory, unless otherwise specified
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.

The study objectives, endpoints, and estimands are detailed below.

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

Objectives	Estimands	Endpoints
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
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

Objectives	Estimands	Endpoints
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 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 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
	• 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 CCI cases with associated per-protocol ILI caused by any strain
	• 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 RT-PCR, 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 RT-PCR, local RT-PCR, or culture, with associated per-protocol ILI

Objectives	Estimands	Endpoints
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 HAIs 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 HAIs CCI for the influenza strains that are present in the study interventions: • 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 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 HAIs 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 HAIs CCI for the influenza strains that are present in the study interventions: • 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 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 HAIs CCI [redacted]: • 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 [redacted] influenza vaccines • HAI titers for the 2022-2023 northern hemisphere seasonal strains (2×A, 2×B) recommended by WHO for CCI [redacted] influenza vaccines • HAI titers for the 2023 southern hemisphere seasonal strains (2×A, 2×B) recommended by WHO for CCI [redacted] influenza vaccines • HAI titers for the 2023 southern hemisphere seasonal strains (2×A, 2×B) recommended by WHO for CCI [redacted] influenza vaccines

Objectives	Estimands	Endpoints
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
CCI		

Objectives	Estimands	Endpoints
CCI	[redacted]	[redacted]

Objectives	Estimands	Endpoints
CCI		

There are no primary immunogenicity objectives in this study.

For the purposes of the study estimands:

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

4. STUDY DESIGN

4.1. Overall 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 initially 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 proceed only if regulatory authority endorsement is obtained to do so. Enrollment into each of the 2 age strata (18 through 64 and ≥65 years of age) may therefore occur independently. Based on Phase 2 safety and immunogenicity data, the dose level of qIRV by age stratum is CCI µg for participants 18 through 64 years of age and CCI µg for participants ≥65 years of age.
- 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. 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. An additional optional blood sample of 50 mL may be collected from participants who consent to the time points specified in Section 1.3 for assessment of CCI; the number of participants asked to provide these samples will be determined by Pfizer, contingent on operational considerations.
  - 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.

Up to approximately CCI additional participants may be enrolled during the second season and randomized CCI to receive 1 dose of either qIRV or seasonal QIV comparator. Of these additional participants:

- The number of participants 18 through 64 or ≥65 years of age will be determined by Pfizer based on enrollment in each of these age strata during the 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 at 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 CCI [redacted]. Within each age stratum, hypothesis testing relating to the VE and immunogenicity objectives will occur in a hierarchical manner as described in Section 9.1.4.

If the primary efficacy analysis for qIRV is not favorable, at the sponsor's discretion, the study may be unblinded early and, if still during the influenza season, participants who were randomized to receive qIRV may be offered a licensed QIV.

Following vaccination, for all participants, AEs will be collected from informed consent signing through 4 weeks following vaccination, and SAEs will be collected from informed consent signing through 6 months after vaccination. In addition, AEs occurring up to 48 hours after blood draws or collection of midturbinate swabs will be collected. Deaths, pneumonia, and hospitalizations related to ILIs will be recorded for the entire study duration.

Up to approximately 53,200 participants may be enrolled in the study in total.

4.2. Scientific Rationale for Study Design

See Section 2.1 and Section 2.2.4.

4.2.1. Diversity of Study Population

See Section 5.

4.2.2. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for the modRNA influenza vaccines used in this study, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. The use of a highly effective method of contraception is required for sexual intercourse involving a WOCBP (see Appendix 3).

4.3. Justification for Dose

In participants 65 through 85 years of age, similar or higher antibody responses and T-cell responses were observed to all 4 strains elicited by a single dose of qIRV (CCI µg) compared to qIRV (CCI µg). A single dose of qIRV up to CCI µg was well tolerated. Based on the totality of data in this study, a single dose of qIRV (CCI µg) was selected as the dose to be evaluated in participants ≥65 years of age in this Phase 3 study (C4781004).

In participants 18 through 64 years of age, antibody and T-cell responses were similar overall between qIRV CCI µg) and qIRV (CCI µg). A modest dose-dependent increase in reactogenicity was observed between the qIRV CCI µg) and qIRV (CCI µg) groups. Based on the totality of data in this study, a single dose of qIRV CCI µg) was selected as the dose to be evaluated in participants 18 through 64 years of age in this Phase 3 study (C4781004).

4.4. End of Study Definition

The end of the study is defined as either the date of the last visit of the last participant in the study, or when the final primary efficacy analysis has been triggered, whichever occurs later.

A participant is considered to have completed the study either when they have completed the last visit (Visit 4) or when the influenza season ends (as judged by Pfizer based on epidemiological data), whichever occurs later.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

Individual participants may not be enrolled in this study more than once.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization.

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants ≥18 years of age (or the minimum age of consent in accordance with local regulations) at Visit 1 (Day 1).

    - Refer to Appendix 3 for reproductive criteria for male (Section 10.3.1) and female (Section 10.3.2) participants.

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

2. Participants who are willing and able to comply with all scheduled visits, investigational plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

    Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.9.

4. Capable of giving signed informed consent as described in the protocol, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality, that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. History of severe adverse reaction associated with any vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

3. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

   Note: Individuals who have had a splenectomy or have functional asplenia will be considered ineligible.

4. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

5. Allergy to egg proteins (egg or egg products) or chicken proteins.

Prior/Concomitant Therapy:

6. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

7. Receipt of blood/plasma products or immunoglobulin from 60 days before study intervention administration, or planned receipt throughout the study.

8. Vaccination with any investigational or licensed influenza vaccine within 6 months (175 days) before study intervention administration, or ongoing receipt of chronic antiviral therapy with activity against influenza.

9. Any participant who has received or plans to receive a modRNA-platform SARS-CoV-2 vaccine within 14 days before or after study vaccination at Visit 1.

Prior/Concurrent Clinical Study Experience:

10. Participation in other studies involving administration of a study intervention within 28 days prior to, and/or during, participation in this study.

    Note: In addition to administration of investigational products, study interventions may include additional procedures, such as collection of biological samples. Therefore, participants may not be in another study whereby procedures, such as respiratory illness visits, may interfere with compliance with this study's protocol.

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

11. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 3, Section 10.3.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use acceptable effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

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

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

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

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

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

2. Receipt of any nonstudy vaccine within 14 days before study intervention administration at Visit 1.

3. Anticipated receipt of any nonstudy vaccine within 14 days after study intervention administration at Visit 1.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration at Visit 1 should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1. Study Intervention(s) Administered

Study interventions for this study will be:

Study Interventions		
Intervention Name	**qIRV**	**QIV**
Type	Vaccine	Vaccine
Targeted influenza strains	For each season - strains as recommended by WHO for influenza vaccines.	For each season - strains as recommended by WHO for influenza vaccines.

Study Interventions		
Intervention Name	**qIRV**	**QIV**
Unit dose strength(s)	Based on Phase 2 safety and immunogenicity data, the dose level of qIRV by age stratum is [redacted] µg for participants 18 through 64 years of age and [redacted] µg for participants ≥65 years of age.	As detailed in the IPM
Route of administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Comparator
IMP or NIMP (global designation)	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor or locally by the trial site (local sourcing by the trial site is not permitted without sponsor approval)
Packaging and labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided as either a PFS or a glass vial as open-label supply. Each dispensable unit will be labeled per country requirement.

If the primary efficacy analysis is not favorable, at the sponsor's discretion, the study may be unblinded early and, if still during the influenza season, participants who were randomized to receive qIRV may be offered a licensed QIV. This QIV will be considered NIMP, sourced locally by site and administered per the local package insert.

6.1.1. Administration

Participants will receive 1 dose of either qIRV or QIV as randomized at Visit 1 in accordance with the study's SoA (Section 1.3). Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm. Study intervention will be administered only by an **unblinded** administrator.

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

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

Study intervention administration details will be recorded on the CRF.

6.1.2. Medical Devices

The comparator vaccines detailed in Section 6.1 may be provided as PFSs and, in which case, should be considered medical devices.

All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.9) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

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

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

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. See the IPM for allowable storage conditions of prepared study intervention.

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

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

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

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

6.2.1. Preparation and Dispensing

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

Study intervention will be prepared by qualified unblinded site personnel according to the IPM or package insert, and the study intervention will be administered in such a way as to ensure the participants remain blinded.

6.3. Assignment to Study Intervention

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

Study intervention will be dispensed at the study visits summarized in the SoA.

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

6.4. Blinding

This is an observer-blinded study.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

The study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator and investigator staff, will be blinded to assignment of study intervention. In particular, the individuals who evaluate participant safety will be blinded. Because there are differences in physical appearance of qIRV and QIV, these study interventions will be administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4.3. Blinding of the Sponsor

The majority of sponsor staff will be blinded to study intervention allocation during the study. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor/Pfizer staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

- Unblinded clinician(s) who are not direct members of the study team and will not participate in any other study-related activities will review unblinded protocol deviations.

- A team supporting interactions with, and analyses for, the DMC (see Section 10.1.5) will be unblinded.

- An unblinded submissions team may be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers who will become unblinded at the participant level at the time of such a reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not

have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after such an analysis.

The study will be unblinded to all sponsor/Pfizer staff when the study is completed.

6.4.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's study intervention assignment unless this could delay further management of the participant. If a participant's study intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

6.5. Study Intervention Compliance

Participants will be dosed at the site and they will receive study intervention directly from the unblinded administrator. The date and time of each dose administered in the clinic will be recorded in the source documents and CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6. Dose Modification

Not applicable.

6.7. Continued Access to Study Intervention After the End of the Study

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

6.8. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs as medically appropriate and at least until the next scheduled follow-up.

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

6.9. Prior and Concomitant Therapy

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, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

6.9.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 14 days before and 14 days after study vaccination at Visit 1.
- Receipt of any mRNA-platform SARS-CoV-2 vaccine within 14 days before and 14 days after study vaccination at Visit 1.
- Receipt of any other (nonstudy) seasonal influenza vaccine at any time during study participation is prohibited.
- Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study is prohibited.
- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment through 28 days after administration of the study intervention.

- Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study is prohibited.

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

6.9.2. Permitted During the Study

- Medication other than that described as prohibited in Section 6.9.1 required for treatment of preexisting conditions or acute illness is permitted.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety and immunogenicity. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed. Participants who remain in the study for safety evaluation will be contacted by telephone at 1 month and 6 months after their last study vaccination to record AEs and SAEs as described in Section 8.10.4 and Section 8.10.5, respectively.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;

- Lost to follow-up;

- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

The date of birth (as permitted by local regulations) will be collected to critically evaluate the immune response and safety profile by age.

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

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

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive

actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

For participants in the immunogenicity subset, the minimal blood sampling volume is approximately 45 mL (15 mL at Visits 1, 3, and 4). Approximately [redacted] participants will be asked to consent to alternatively providing approximately 150 mL (50 mL at Visits 1, 3, and 4), which will be used for immunogenicity assessments and assay development. Additional optional whole blood samples of approximately 50 mL at Visits 1, 2, 3, and 4 will be obtained from participants who consent for [redacted] as detailed in Section 4.1.

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

8.1.1. Telehealth Visits

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

- Procedures as indicated for Visit 4 (see Section 8.10.5). For participants not included in the immunogenicity subset only.
- Procedures as indicated for ILI visits (Section 8.10.6.1).

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

8.1.2. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit (see the SoA):

- Procedures as indicated for Visits 2, 3, and 4 (see Section 8.10.3, Section 8.10.4, and Section 8.10.5, respectively)

- Procedures as indicated for ILI visits (Section 8.10.6.1)

8.2. Efficacy and/or Immunogenicity Assessments

8.2.1. Surveillance for Influenza

Following vaccination, if a participant develops symptoms of per-protocol ILI as detailed in Section 8.10.6, the participant should contact the site and an in-person, home health, or telehealth ILI visit should occur within 5 days of onset of ILI symptoms (see Section 8.10.6.1). At the ILI visit, assessments should be conducted as specified in Section 8.10.6.1, which will include collection of 2 midturbinate swab samples (1 from each nostril) for testing at a central laboratory using RT-PCR and viral culture testing to detect influenza viruses in the respiratory specimen. CCI [redacted] (Cepheid Xpert Xpress CoV-2/Flu/RSV plus test).

Culture testing will only be conducted on swab samples from participants with an RT-PCR–positive swab sample from the corresponding ILI visit.

Midturbinate swabs will be collected by site staff if the ILI visit is conducted in person, or midturbinate swabs will be collected by the participant if the ILI visit is conducted as a telehealth consultation.

Both the central laboratory RT-PCR and viral culture results will be used for the relevant endpoint case definitions as shown in Table 1. Local test results for influenza will also be collected at the ILI visit, if available.

ILIs and their sequelae (including pneumonia and death) that are consistent with the clinical endpoint definition should not be recorded as AEs (see Section 8.4.7 for further details).

8.2.1.1. Antigenic Characterization of Influenza Viruses

An HAI, also 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. A vaccine-matched (antigenically similar) strain is defined as a CCI [redacted] difference in HAI titers relative to a reference serum. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.10.6.1) will be assessed.

8.2.1.2. ILI Memory Aid

Participants will be given a memory aid at Visit 1 that may be used to note the severity and duration of ILI symptoms between the time of ILI onset and the ILI visit. These memory aids may be used to assist in the reporting and discussion of ILI symptoms with study staff but will not be considered source documents and will not be collected at study visits. Only information collected by study staff as part of the ILI visit will be included in the source documents and entered into the CRF.

8.2.2. Immunogenicity Assessments

Samples will be collected at time points specified in Section 1.3 and Section 9.6.2 from participants in the immunogenicity subset, and the following assays will be run:

- HAI titers against seasonal strains (2×A, 2×B) recommended by WHO for CCI influenza vaccines.
- HAI titers against seasonal strains (2×A, 2×B) recommended by WHO for CCI [redacted] influenza vaccines.

Not all samples collected from participants in the immunogenicity subset will be tested using HAIs CCI [redacted] at every visit. As described in Section 9.6.2, at prespecified time points, samples will be randomly selected from the immunogenicity subsets in northern and southern hemispheres. The subsets of samples required for the immunogenicity assessments will be generated by an unblinded, independent statistician.

CCI [redacted]

CCI [redacted] Some of the samples may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs for understanding the B-cell, T-cell, and antibody repertoires.

8.2.3. Biological Samples

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

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

8.3. Safety Assessments

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

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

AEs and SAEs are collected, recorded, and reported as defined in Section 8.4.

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

Safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever) and use of antipyretic medication that occur in the 7 days after administration of the study intervention from participants in the reactogenicity subset. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.3.4.

8.3.1. Physical Examinations

A physical examination may be performed at Visit 1 prior to vaccination, if clinically indicated. Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 2) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

The participant's oral temperature will be measured prior to vaccination. Additionally, weight and height will 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 (Appendix 2) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3. Clinical Safety Laboratory Assessments

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

8.3.4. Reactogenicity Electronic Diary (Reactogenicity Subset Participants Only)

Participants in the reactogenicity subset will be required to complete a reactogenicity e-diary through an application installed on a provisioned device or on the participant's own personal device. These participants will be asked to monitor and record local reactions, systemic

events, and use of antipyretic medication for 7 days, where Day 1 is the day of study intervention administration.

The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

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

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

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

All other participants will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.4.2.

8.3.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events collected by e-diary as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[26]

Confirmed Grade 4 reactions must be entered on the participant's AE log and be evaluated for SAE reporting.

8.3.4.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information and the corresponding resolution date. The investigator will enter this resolution date in the CRF.

Participants will be provided with a measuring device. Redness and swelling will be measured and recorded in CCI [redacted] and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 2. 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 2.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor.

Table 2. Local Reaction Grading Scale

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

8.3.4.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 3.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor.

Table 3. Systemic Event Grading Scale

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

Table 3. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

8.3.4.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 4 during analysis.

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

Table 4. Scale for Fever

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

8.3.4.5. Antipyretic Medication

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

8.3.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at Visit 1, before the administration of the dose of study intervention. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will not be administered the study intervention and will be withdrawn from the study.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Section 10.2.

The definitions of device-related safety events (ADEs and SADEs) can be found in Section 10.8. Device deficiencies are covered in Section 8.4.9.

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

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

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 3. In addition, AEs occurring up to 48 hours after blood draws or collection of

midturbinate swabs must be recorded on the CRF. SAEs will be collected from the time the participant provides informed consent to Visit 4 (approximately 6 months after vaccination).

Deaths, pneumonia, and hospitalizations will be recorded as follows:

a. If related to ILIs (as defined in Section 8.10.6) or their sequelae: these events will be recorded for the entire study duration on the relevant CRF page related to the ILI visit and will not be reported as SAEs/AEs (see Section 8.4.7).

b. If not related to ILIs or their sequelae: these events will be reported as AEs/SAEs as appropriate up to Visit 4.

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Section 10.2. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

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

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

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

8.4.3. Follow-Up of AEs and SAEs

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

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

Further information on follow-up procedures is provided in Section 10.2.

8.4.4. Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

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

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

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then inseminates his female partner prior to or around the time of conception.

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

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

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

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

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

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

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

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

the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Deaths will be recorded throughout the study as detailed in Section 8.4.1.

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

ILIs and their sequelae, including pneumonia and death, that are potentially consistent with any clinical efficacy endpoint definitions should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

ILIs and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the ILI visit pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

ILIs and their sequelae will be reviewed by an internal blinded case reviewer. Any SAE that is determined by the internal case reviewer NOT to meet any clinical primary efficacy endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.4.8. Adverse Events of Special Interest

The following events are considered AESIs:

- A confirmed diagnosis of myocarditis or pericarditis. See Section 8.10.8 for additional procedures for monitoring of potential myocarditis or pericarditis.

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Reporting Form.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.1.2. In order to fulfill regulatory reporting obligations worldwide, the unblinded site staff is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.8.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.4.1 through 8.4.4 and Section 10.2 of the protocol.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

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

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

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

The method of documenting medical device deficiencies is provided in Section 10.8.

8.4.9.2. Follow-Up of Medical Device Deficiencies

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

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

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

8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

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

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

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

4. If an SAE associated with the device deficiency is brought to the attention of the unblinded site staff, the unblinded site staff must immediately notify Pfizer Safety of the SAE (see Section 8.4.1.1). All relevant details related to the role of the device in the event must be included in the Vaccine SAE Reporting Form as outlined in Sections 8.4.1.1 and 8.4.1.2.

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

8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies

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

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

8.4.10. Vaccination Errors

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

Vaccinations errors are recorded and reported as follows:

Recorded on the Vaccination Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the Vaccination error	Only if associated with an SAE

Vaccination errors include:

- Vaccination errors involving participant exposure to the study intervention;
- Potential vaccination errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;

- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

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

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

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

8.6.1. Specified Genetics

Some of the blood samples collected for CCI [redacted] may be used for CCI [redacted]. The CCI [redacted]

CCI [redacted] See Section 10.4 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.2.2.

8.9. CCI [redacted]

CCI [redacted]

Details will be specified in the SAP.

8.10. Study Procedures

8.10.1. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant and the study site staff will be established. The participant may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant to report whether or not the participant has experienced ILI symptoms and/or medically attended events for an ILI, eg, telephone consultation with a medical practitioner, doctor's visit, emergency room visit, or hospitalization (ILI e-diary; see Section 8.10.6).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- Message to confirm that study participation and/or ILI surveillance has completed.
- A platform for recording local reactions and systemic events (reactogenicity e-diary; see Section 8.3.4).

The investigator or designee will review ILI e-diary data online at frequent intervals following vaccination to evaluate participant compliance and as part of the ongoing safety review. If a participant is not actively completing either the reactogenicity or ILI e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

8.10.2. Visit 1 – Vaccination (Day 1)

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

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

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected (as permitted by local regulations) to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- On the day of and prior to study intervention administration, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record findings on the medical history CRF.
- Measure the participant's height and weight.
- On the day of and prior to study intervention administration, measure the participant's oral temperature.
- Record prior receipt of any COVID-19 vaccine as described in Section 6.9.
- Record prior receipt of any pneumococcal vaccine as described in Section 6.9.
- Record licensed influenza vaccine information, if received during the prior calendar year, as described in Section 6.9.
- Record nonstudy vaccinations as described in Section 6.9.
- On the day of and prior to study intervention administration, perform urine pregnancy test on WOCBP as described in Section 8.3.5.
- If applicable, discuss contraceptive use as described in Section 4.2.2.
- On the day of and prior to study intervention administration, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- On the day of and prior to study intervention administration, ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- On the day of and prior to study intervention administration, obtain the participant's randomization number and study intervention allocation using the IRT system.
- On the day of and prior to study intervention administration, for participants in the immunogenicity subset, collect a blood sample (approximately 15 mL), before administration of study intervention, for immunogenicity assessment. Alternatively, if the participant has consented to do so, collect a blood sample of approximately 50 mL, rather than 15 mL, before administration of study intervention, for immunogenicity assessment/assay development.
    - If the participant has consented to do so, collect a blood sample (approximately 50 mL) for CCI [redacted].
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the (preferably) nondominant arm. Please refer to the IPM for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents, on the AE CRF, and on an SAE form as applicable.
- Provide self-swab kits and instructions on self-collection of midturbinate swabs.
- Explain the e-diary technologies available for this study (see Section 8.10.1), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
- For participants in the reactogenicity subset:
    - Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.
    - Provide a measuring device to measure local reactions at the injection site.
    - Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
        - Fever ≥39.0°C (≥102.1°F).

- Redness or swelling at the injection site measuring greater than 10 cm CCI [redacted]
- Severe pain at the injection site.
- Any severe systemic event.

- Provide instructions on ILI e-diary completion and ask the participant to complete the ILI e-diary if the participant experiences symptoms of ILI and when he/she receives a reminder – this will be at least weekly. See Section 8.10.1 for further details.
- Provide a thermometer for recording daily temperatures (reactogenicity subset participants) and fever (ILI surveillance); provide instructions on their use.
- Provide the participant with an ILI memory aid (Section 8.2.1.2) and instruct the participant to use the memory aid between the time of ILI symptom onset and an ILI visit to record the severity of ILI symptoms and their duration.
- Record AEs as described in Section 8.4.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the ILI e-diary) immediately if he or she experiences any ILI symptoms as detailed in Section 8.10.6.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.8).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

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

8.10.3. Visit 2 – 1-Week Follow-Up Visit (After Vaccination) – 6 to 8 Days After Visit 1

Visit 2 will only be conducted for participants who have consented to provide the optional blood sample for CCI [redacted]. Visit 2 may be completed as a home health visit (see Section 8.1.2).

- Record AEs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 6.9.
- Record prohibited medication use as described in Section 6.9.1.
- If applicable, discuss contraceptive use as described in Section 4.2.2.
- Collect a blood sample (50 mL) for CCI [redacted].
- For participants in the reactogenicity subset:
  - Review the participant's reactogenicity e-diary data. If the e-diary collection period is complete, collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
  - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm CCI [redacted]
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.8).
- Ask the participant to contact the site staff or investigator (this could be via the ILI e-diary) immediately if he or she experiences any ILI symptoms as detailed in Section 8.10.6.

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.4. Visit 3 – 4-Week Follow-Up Visit (After Vaccination) – 28 to 35 Days After Visit 1

Visit 3 may be completed as a home health visit (see Section 8.1.2).

- Record AEs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 6.9.
- Record prohibited medication use as described in Section 6.9.1.
- If applicable, discuss contraceptive use as described in Section 4.2.2.
- For participants in the immunogenicity subset, collect a blood sample of approximately 15 mL for immunogenicity testing. Alternatively, if the participant has consented to do so, collect a blood sample of approximately 50 mL, rather than 15 mL, for immunogenicity assessment/assay development.
    - If the participant has consented to do so, collect a blood sample (50 mL) for CCI [redacted]
- For participants in the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the ILI e-diary) immediately if he or she experiences any ILI symptoms as detailed in Section 8.10.6.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.4.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.5. Visit 4 – 6-Month Follow-Up Visit (After Vaccination) – 175 to 189 Days After Visit 1

Visit 4 may be conducted as a home health visit for all participants (see Section 8.1.2). For participants not included in the immunogenicity subset, Visit 4 may be conducted as a telehealth visit (see Section 8.1.1).

- Record SAEs and pneumonia as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 6.9.
- Record prohibited medication use as described in Section 6.9.1.
- For participants in the immunogenicity subset, collect a blood sample of approximately 15 mL for immunogenicity testing. Alternatively, if the participant has consented to do so, collect a blood sample of approximately 50 mL, rather than 15 mL, for immunogenicity assessment/assay development.
    - If the participant has consented to do so, collect a blood sample (50 mL) for CCI [redacted]
- Ask the participant to contact the site staff or investigator (this could be via the ILI e-diary) immediately if he or she experiences any ILI symptoms as detailed in Section 8.10.6.
- If directed by Pfizer (eg, at the end of the influenza season), collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device; if Visit 4 is being conducted as a telehealth visit and the participant has a provisioned e-diary device, ask them to return this by mail.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.4.

8.10.6. ILI Surveillance (All Participants)

If a participant experiences an 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 (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, within 5 days after symptom onset.

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

- CCI
- [redacted]

Systemic symptoms:

- CCI
- [redacted]

Surveillance of potential ILI symptoms should continue even if a participant has a positive RT-PCR or culture test result earlier in the study.

During the 7 days following vaccination, ILI symptoms that overlap with specific systemic events (ie, fever, chills, fatigue/tiredness, new or increased muscle pain [myalgia], or headache) should not trigger an ILI visit unless, in the investigator's opinion, the clinical picture is more indicative of ILI than vaccine reactogenicity.

Participants may utilize an ILI e-diary through an application (see Section 8.10.1) installed on a provisioned device or on the participant's personal device to prompt him/her weekly to report any symptoms and medically attended events (eg, telephone consultation with a medical practitioner, doctor's visit, emergency room visit, or hospitalization) that occur for the ILI. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

The sponsor may increase or decrease the frequency of the weekly contacts or the duration of surveillance for ILI based on influenza surveillance data or other operational factors.

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.

8.10.6.1. ILI Visit (Within 5 Days After ILI Onset)

This visit may be conducted as an in-person (eg, at the study site, or in the participant's home (home health visit, see Section 8.1.2) or telehealth visit (see Section 8.1.1); a telehealth visit involves the sharing of healthcare information and services via appropriate telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's ILI may evolve over time, several contacts may be required to obtain the following information:

- If needed, provide self-swab kits and instructions on self-collection of midturbinate swabs.
- If the visit is conducted in person, obtain 2 midturbinate swabs (collected by site staff), 1 from each nostril. Alternatively, if conducted by telehealth, instruct the participant to self-collect 2 midturbinate swabs, 1 from each nostril, and ship to the central laboratory for assessment.
- Perform clinical assessment, including temperature and, if the ILI visit is being conducted in person, respiratory rate. Collect details of any ILI symptoms reported by the participant (if used, the participant may refer to the ILI memory aid to recall details of these symptoms) or noted via clinical assessment, including severity (see Section 10.2.3) and duration of
  - CCI [redacted]

- Following ILI symptom resolution, confirm, based on the participant's own assessment:
  - Has the participant returned to the same level of health as prior to the onset of ILI?
  - Is the participant able to conduct daily activities as prior to the onset of ILI?
  - Has the participant required nonprofessional (eg, family member) assistance for ILI?
- Collect ILI-related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Number and type of any healthcare contact; duration of hospitalization and ICU stay; date of visit.
  - Mechanical ventilation use (if applicable).
  - Oxygen saturation.
  - Oxygen use (if applicable).
  - Local test results for influenza and any local noninfluenza respiratory pathogen testing, including the trade name of the testing platform used.
  - Results of x-rays or CT scans if performed.
  - Clinical diagnosis and sequelae, eg, pneumonia.
  - Concomitant medications used to treat ILI symptoms.
  - Death.
- Record nonstudy vaccinations as described in Section 6.9.
- Discuss contraceptive use as described in Section 4.2.2.
- Record prohibited medication use as described in Section 6.9.1.
- Record any AEs that occur within the 48 hours after the midturbinate swab as described in Section 8.4.
- Record AEs as described in Section 8.4. Note: ILIs and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs (see Section 8.4.7 for further details). These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.10.7. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction (Reactogenicity Subset Participants Only)

If a Grade 3 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever (Section 8.3.4.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever (Section 8.3.4.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets Grade 4 criteria.

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

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

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

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

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

- Measure oral temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.3.4.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.3.4.3.

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

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

8.10.8. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 14 days after the study intervention administration should be specifically evaluated for possible myocarditis or pericarditis.

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

- ECG and
- Measurement of the troponin level

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

- Evaluation by a cardiologist,
- Cardiac echocardiogram, and/or
- Cardiac magnetic resonance study

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

An evaluation is not required if, in the investigator's opinion, the symptoms reported are more indicative of ILI. In that case, the procedures described in Section 8.10.6 should be performed.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

The hypotheses for the primary efficacy objectives (2 for each age stratum) and secondary immunogenicity objectives are stated below.

9.1.1. Efficacy

The primary efficacy objectives of this study are to evaluate the noninferiority and 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 in each age stratum (participants 18 through 64 and ≥65 years of age) independently.

The statistical hypotheses are defined below, and the evaluable efficacy population will be used for hypothesis testing. The order in which these hypotheses will be tested is detailed in Section 9.1.4.

9.1.1.1. Noninferiority of Efficacy

The following hypothesis for noninferiority 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 stratum independently (participants 18 through 64 and ≥65 years of age).

H_0: RVE CCI

CCI

H_0: p CCI

9.1.1.2. Superiority of Efficacy

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 stratum independently (participants 18 through 64 and ≥65 years of age).

H_0: RVE CCI

9.1.2. 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 HAIs CCI [redacted], 2 statistical hypotheses for each targeted strain will be defined as described below, and the evaluable immunogenicity population (HAIs CCI [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 HAIs CCI [redacted] 2 statistical hypotheses for each targeted strain will be defined as described above based on the evaluable immunogenicity population (HAIs CCI [redacted].

Note: There are no primary immunogenicity objectives in this study.

9.1.3. Estimands

9.1.3.1. Primary Estimands/Coprimary Estimands

The primary estimands corresponding to each primary objective are described in the table in Section 3.

The estimand to evaluate the efficacy objective is primarily based on the evaluable efficacy population. This estimand estimates the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. For participants who are lost to follow-up, discontinue from the study, or have major protocol violations, all post–follow-up, postdiscontinuation, or postviolation observations will be censored.

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

9.1.3.2. Secondary Estimands

The secondary estimands corresponding to each secondary objective are described in the table in Section 3. The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity populations. These estimands estimate the immune response after study intervention administration in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

9.1.4. Multiplicity Adjustment

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. CCI

There are 2 hypothesis tests for the primary efficacy objectives in each age stratum (participants 18 through 64 and ≥65 years of age), ie, noninferiority and superiority of efficacy. See Section 9.1.1.1. and Section 9.1.1.2.

There are 8 hypothesis tests for the secondary immunogenicity objectives based on CCI HAIs and CCI HAIs 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 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 (HAIs CCI) 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 HAIs CCI , the hypothesis testing will be performed in their associated strain, CCI . The hypotheses related to the secondary immunogenicity objective assessed using HAIs CCI for each age stratum will be tested in the same order as CCI (CCI) after the secondary immunogenicity objective (HAIs CCI) in the respective age stratum has been achieved.

CCI

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

All VE 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.

9.2. Analysis Sets

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

Population	Description
Screened	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity (HAIs CCI)	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 after vaccination, have at least 1 valid and determinate assay result (HAIs CCI) at the 4-week postvaccination visit, and have no major protocol violations.
Evaluable immunogenicity (HAIs CCI)	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 after vaccination, have at least 1 valid and determinate assay result (HAIs CCI) at the 4-week postvaccination visit, and have no major protocol violations.
mITT immunogenicity (HAIs CCI)	All randomized participants in the immunogenicity subset who receive the study intervention and have at least 1 valid and determinate assay result (HAIs CCI) after vaccination.
mITT immunogenicity (HAIs CCI)	All randomized participants in the immunogenicity subset who receive the study intervention and have at least 1 valid and determinate assay result (HAIs CCI) after vaccination.
Evaluable efficacy	All participants who are eligible, receive the study intervention to which they were randomized, and have no major protocol violations before the symptom onset date of the confirmed LCI case, starting at least 14 days after vaccination, and associated with a per-protocol ILI.

Population	Description
mITT efficacy	All randomized participants who receive the study intervention.
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 transferred for reactogenicity.

9.3. Statistical Analyses

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

9.3.1. General Considerations

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

For all the efficacy endpoints, the analyses will be performed on both the evaluable efficacy population and the mITT efficacy population; the main analysis will be based on the evaluable efficacy population. Participants will be summarized according to the vaccine group to which they were randomized for the mITT efficacy population.

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

For all the immunogenicity endpoints (HAIs CCI), the analysis will be based on the evaluable immunogenicity populations. Antibody titers below the LLOQ or denoted as BLQ will be set to CCI for immunogenicity analysis. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ.

An additional analysis may be performed based on the mITT immunogenicity populations (HAIs CCI if there is a large enough difference in sample size between the mITT immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

9.3.1.1. Analyses for Binary Data

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

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

The 3-tier approach may be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

9.3.1.2. Analyses for Continuous Data

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

9.3.1.2.1. Geometric Means

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

9.3.1.2.2. Geometric Mean Fold Rises

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

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

9.3.1.2.3. Geometric Mean Ratios

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

9.3.1.2.4. Reverse Cumulative Distribution Curves

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

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Primary efficacy (participants ≥65 years of age)	• RVE, defined as the relative risk reduction of the proportion of participants reporting first-episode LCI cases with associated per-protocol ILI caused by any strain, with symptom onset at least 14 days after vaccination, in the qIRV group compared to the QIV group, will be estimated along with the 2-sided 95% CI for the age stratum with participants ≥65 years of age. • The analysis of efficacy will use a conditional exact test based on the binomial distribution of the number of first-episode LCI cases in the qIRV group, given the total number of first-episode cases in both groups. • If the lower confidence limit of 95% for RVE with participants ≥65 years of age at the final analysis exceeds [redacted], the null hypothesis for the RVE noninferiority objective will be rejected. • If the lower confidence limit of 95% for RVE with participants ≥65 years of age at the final analysis exceeds [redacted], the null hypothesis for the RVE superiority objective will be rejected. • The evaluable efficacy population will be the primary population for efficacy analyses. The analysis will be repeated on the mITT efficacy population. • Sensitivity analysis on the primary endpoint using different method(s) to estimate RVE, such as by the Cox proportional hazards model, may be explored in the SAP.
Primary efficacy (participants 18 through 64 years of age)	• RVE, defined as the relative risk reduction of the proportion of participants reporting first-episode LCI cases with associated per-protocol ILI caused by any strain, with symptom onset at least 14 days after vaccination, in the qIRV group compared to the QIV group, will be estimated along with the 2-sided 95% CI for the age stratum with participants 18 through 64 years of age. • The analyses for efficacy with participants 18 through 64 years of age will use the exact conditional binomial method as described above for participants ≥65 years of age.

Endpoint	Statistical Analysis Methods
	• If the lower confidence limit of 95% for RVE with participants 18 through 64 years of age at the final analysis exceeds [redacted], the null hypothesis for the RVE noninferiority objective will be rejected. • If the lower confidence limit of 95% for RVE with participants 18 through 64 years of age at the final analysis exceeds [redacted], the null hypothesis for the RVE superiority objective will be rejected. • The evaluable efficacy population will be the primary population for efficacy analyses. The analysis will be repeated on the mITT efficacy population. • Sensitivity analysis on the primary endpoint using different method(s) to estimate RVE, such as by the Cox proportional hazards model, may be explored in the SAP.
Primary safety (participants 18 through 64 years of age and ≥65 years of age)	• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (local reactions, systemic events, AEs, and SAEs) for each vaccine group by age stratum (participants 18 through 64 and ≥65 years of age). • Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting AEs and SAEs for the overall population (participants ≥18 years of age). • AEs and SAEs will be categorized according to MedDRA terms. A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are [redacted] of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. Descriptive summary statistics (counts and proportions) will be provided for Tier 3 events for each vaccine group. Analysis methods are described in Section 9.3.1.1.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Secondary efficacy (qIRV compared to QIV against LCI or CCI associated with different definitions of ILI with participants 18 through 64 years of age and ≥65 years of age)	The analysis of the following RVEs based on various case definitions will use the exact conditional binomial method, as described for the above efficacy endpoint based on per-protocol ILI. RVE will be estimated along with 2-sided 95% CI by age stratum (participants 18 through 64 and ≥65 years of age). • RVE, defined as the relative reduction of the proportion of participants reporting first-episode LCI cases with associated per-protocol ILI caused by all matched strains, with onset at least 14 days after vaccination, in the qIRV group compared to the QIV group. • RVE, defined as the relative reduction of the proportion of participants reporting first-episode LCI cases with associated per-protocol ILI caused by each matched strain, with onset at least 14 days after vaccination, in the qIRV group compared to the QIV group. • RVE, defined as the relative reduction of the proportion of participants reporting first-episode LCI cases with associated per-protocol ILI caused by all unmatched strains, with onset at least 14 days after vaccination, in the qIRV group compared to the QIV group. • RVE, defined as the relative reduction of the proportion of participants reporting first-episode CCI cases associated with per-protocol ILI caused by any strain, with onset at least 14 days after vaccination, in the qIRV group compared to the QIV group. • RVE, defined as the relative reduction of the proportion of participants reporting first-episode LCI cases associated with ILI (as defined by applying a modified CDC definition) caused by any strain, with onset at least 14 days after vaccination, in the qIRV group compared to the QIV group. • RVE, defined as the relative reduction of the proportion of participants reporting first-episode LCI cases associated with ILI (as defined by applying the WHO definition) caused by any strain, with onset at least 14 days after vaccination, in the qIRV group compared to the QIV group. • RVE, defined as the relative reduction of the proportion of participants reporting first-episode influenza cases associated with ILI ([redacted]), with onset at least 14 days after vaccination, in the qIRV group compared to the QIV group.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity (HAIs CCI [redacted]) (NI assessment of qIRV compared to QIV in participants 18 through 64 years of age and ≥65 years of age)	• GMRs of HAI titers for each strain in qIRV recipients compared to QIV recipients 4 weeks after vaccination and associated 2-sided 95% CIs will be provided by age stratum (18 through 64 or ≥65 years). • The difference in the percentage of participants achieving seroconversion for each strain at 4 weeks after vaccination in qIRV recipients compared to QIV recipients, and associated 2-sided 95% CIs, will be provided by age stratum (18 through 64 or ≥65 years). The 2-sided 95% CIs for the difference in percentages of participants achieving seroconversion between vaccine groups will be calculated using the Miettinen and Nurminen method. • Noninferiority of the immune response elicited by qIRV when compared to QIV will be declared if the lower bounds of the 2-sided 95% CIs for all GMRs are greater than CCI [redacted] and all lower bounds of the 2-sided 95% CI for the difference between vaccine groups in the percentage of participants with seroconversion are greater than CCI [redacted] for each strain. • Only immunogenicity data collected from the CCI [redacted] will be used.
Secondary immunogenicity (HAIs CCI [redacted]) (NI assessment of qIRV compared to QIV in participants 18 through 64 years of age and ≥65 years of age)	• GMRs of HAI titers for each strain in qIRV recipients compared to QIV recipients 4 weeks after vaccination and associated 2-sided 95% CIs will be provided by age stratum (18 through 64 or ≥65 years). • The difference in percentage of participants achieving seroconversion for each strain at 4 weeks after vaccination in qIRV recipients compared to QIV recipients, and associated 2-sided 95% CIs, will be provided by age stratum (18 through 64 or ≥65 years). The 2-sided 95% CIs for the difference in percentages of participants achieving seroconversion between vaccine groups will be calculated using the Miettinen and Nurminen method. • Noninferiority of the immune response elicited by qIRV when compared to QIV will be declared if the lower bounds of the 2-sided 95% CI for all GMRs are greater than CCI [redacted] and all lower bounds of the 2-sided 95% CI for the difference between vaccine groups in the percentage of participants with seroconversion are greater than CCI [redacted] for each strain. • Only immunogenicity data collected from the CCI [redacted] will be used.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity (participants 18 through 64 years of age and ≥65 years of age)	• HAI GMTs and their associated 2-sided 95% CIs will be provided for each strain, by vaccine group, at Day 1 and 4 weeks after receipt of study intervention for participants enrolled in the northern hemisphere and southern hemisphere, separately, by age stratum (18 through 64 or ≥65 years). • HAI GMFRs from before vaccination to 4 weeks after vaccination and their associated 2-sided 95% CIs will be provided for each strain, for participants enrolled in the northern hemisphere and southern hemisphere, separately, by vaccine group and age stratum (18 through 64 or ≥65 years). • 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 before vaccination and at 4 weeks after vaccination, and their associated 2-sided Clopper-Pearson 95% CIs will be provided for participants enrolled in the northern hemisphere and southern hemisphere, separately, by vaccine group and age stratum (18 through 64 or ≥65 years). • The proportion of participants achieving HAI seroconversion for all strains at 4 weeks after vaccination, the proportion of participants with HAI titers ≥1:40 for all strains before vaccination and at 4 weeks after vaccination, and their associated 2-sided Clopper-Pearson 95% CIs will be provided for participants enrolled in the northern hemisphere and southern hemisphere, separately, by vaccine group and age stratum (18 through 64 or ≥65 years). • The above summary statistics will be produced separately for antibody titers measured by CCI [redacted] HAIs.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

Endpoint	Statistical Analysis Methods
CCI [redacted]	[redacted]

Endpoint	Statistical Analysis Methods
CCI	[redacted]

Endpoint	Statistical Analysis Methods
CCI	[redacted]

Endpoint	Statistical Analysis Methods
CCI	[redacted]

9.3.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

Any results from investigation(s) (ECG, troponin level, cardiac echocardiogram, and/or cardiac magnetic resonance study) that might be indicative of myocarditis or pericarditis or an AESI within 14 days after a study vaccination will also be summarized and listed by vaccine group.

9.4. Interim Analyses

There are no formal interim analyses planned for this study.

9.5. Analysis Timing

All safety analyses will be performed on the safety population.

Primary analysis for the younger age stratum (participants 18 through 64 years of age): Analysis of the primary efficacy and secondary 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 analysis may be performed between the primary efficacy and final analysis (Section 6.4.3).

Primary analysis for the older age stratum (participants ≥65 years of age): Analysis of the primary efficacy, safety, and secondary immunogenicity objectives may be conducted when at least CCI first-episode evaluable 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.

Any analyses conducted on Phase 3 data while the study is ongoing will be performed by an unblinded statistical team (see Section 6.4.3).

9.6. Sample Size Determination

9.6.1. Relative Vaccine Efficacy

Up to approximately 36,200 participants CCI [redacted] are planned to be enrolled initially in this study CCI [redacted]

CCI [redacted]

[redacted]

Table 5. CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

9.6.2. Immunogenicity

The antibody titers from participants in the immunogenicity subset will be measured by HAIs CCI [redacted]

Not all samples collected from participants in the immunogenicity subset will be tested using HAIs CCI [redacted] at every visit. As described in Table 6, at prespecified time points, samples will be randomly selected from the immunogenicity subsets in the northern and southern hemispheres. The subsets of samples required for the immunogenicity assessments will be generated by an unblinded, independent statistician.

All participants in the immunogenicity subset CCI [redacted] will have samples tested using HAIs CCI [redacted] at Visit 1 and Visit 3. A subset of up to CCI [redacted] participants in each age stratum will have samples tested using HAIs CCI [redacted] at Visit 1 and Visit 3. Of these CCI [redacted] participants in each age stratum, a further subset will be randomly selected for using HAIs CCI [redacted] at Visit 4.

Table 6. HAIs Used to Evaluate the Immune Responses Against Influenza, by Season

	Visit 1 Vaccination	Visit 3 4-Week Follow-Up Visit	Visit 4 6-Month Follow-Up Visit
2022-2023 Northern Hemisphere Influenza Season			
HAIs CCI [redacted]	Yes (Subset of samples[a])	Yes (Subset of samples[a])	No testing
HAIs CCI [redacted]	Yes (All samples)	Yes (All samples)	Yes (Subset of samples[b])

Table 6. HAIs Used to Evaluate the Immune Responses Against Influenza, by Season

	Visit 1 Vaccination	Visit 3 4-Week Follow-Up Visit	Visit 4 6-Month Follow-Up Visit
2023 Southern Hemisphere Influenza Season			
HAIs CCI [redacted]	Yes (Subset of samples[c])	Yes (Subset of samples[c])	No testing
HAIs CCI [redacted]	Yes (Subset of samples[d])	Yes (Subset of samples[d])	Yes (Subset of samples[d])

a. Samples from a randomly selected subset of participants CCI [redacted] will be tested at Visit 1 and Visit 3 using HAIs CCI [redacted]
b. From the subset of participants randomly selected to have samples tested at Visit 1 and Visit 3 using HAIs CCI [redacted] a select number of these participants will be tested at Visit 4 using HAIs [redacted]
c. Samples from a randomly selected subset of participants in the southern hemisphere will be tested at Visit 1 and Visit 3 using HAIs CCI [redacted]
d. The subset of participants randomly selected to have samples tested using HAIs CCI [redacted] at Visit 1 and Visit 3 will also be tested using HAIs CCI [redacted] at Visit 1, Visit 3, and Visit 4.

9.6.3. Safety

For safety outcomes in the study, Table 7 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, at various sample sizes.

Table 7. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=3000	N=3500	N=6000	N=7000	N=8800	N=9300	N=18,100	N=23,100
0.01%	0.26	0.30	0.45	0.50	0.59	0.61	0.84	0.90
0.03%	0.59	0.65	0.83	0.88	0.93	0.94	>0.99	>0.99
0.05%	0.78	0.83	0.95	0.97	0.99	0.99	>0.99	>0.99
0.07%	0.88	0.91	0.99	0.99	>0.99	>0.99	>0.99	>0.99
0.10%	0.95	0.97	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
0.15%	0.99	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
0.20%	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
0.25%	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
0.32%	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
0.50%	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
1.0%	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
2%	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5%	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10%	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

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

10.1.4. Data Protection

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

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

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. 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.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

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

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

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

10.1.9. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

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

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

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

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

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

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.2.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

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

10.2.2. Definition of an SAE

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

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

Assessment of Intensity

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

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

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

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

10.2.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT. • If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.3. Appendix 3: Contraceptive and Barrier Guidance

10.3.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom when having sexual intercourse with a WOCBP who is not currently pregnant.

  OR

- Be vasectomized, with the absence of sperm having been confirmed.

10.3.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of inclusion criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.3.4 for a complete list of contraceptive methods permitted in the study.

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

- Is not a WOCBP (see definitions below in Section 10.3.3).

  OR

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

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

10.3.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

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

Highly Effective Methods That Are User Dependent

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

    - Oral;

    - Intravaginal;

    - Transdermal.

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

    - Oral;

    - Injectable.

Sexual Abstinence

8. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Other Effective Methods

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

10. Male or female condom, with or without spermicide.

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

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

10.4. Appendix 4: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis. CCI [redacted]
- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
  - Samples for specified genetic analysis (see Section 8.6.1) will be stored for up to 15 years or other period as per local requirements.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

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

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

- Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.6. Appendix 6: Kidney Safety Monitoring Guidelines

10.6.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.6.2. Age-Specific Kidney Function Calculation Recommendations

10.6.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	Scr (mg/dL)	Scys (mg/L)	Recommended eGFR Equation[29]
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr (mg/dL)**	**Scys (mg/L)**	**Recommended eGFR Equation[29]**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.6.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex >120 ms).
• New-onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

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

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

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

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 2 (Section 10.2.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 2 (Section 10.2.2).
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE Definition
• A USADE (also identified as UADE in US Regulations 21 CFR 813.3) is a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

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

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

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the unblinded site staff to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The unblinded site staff will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and will also capture the required information on the Medical Device Complaint form. • It is **not** acceptable for the unblinded site staff to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form. • There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. • If the unblinded site staff determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the unblinded site staff will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. Requirements for recording and reporting an AE or SAE are provided in Appendix 2 (Section 10.2.3).

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

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

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

Follow-Up of Medical Device Deficiency
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the Vaccine SAE Reporting Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 2.

10.8.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Section 10.2.4.

10.8.6. Reporting of SADEs

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

10.9. Appendix 9: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.
    - If CD4 cell count 300-500/mm^3 and HIV RNA suppressed for 2 years, CD4 cell count should have been obtained within 12 months of enrollment.
    - If CD4 cell count >500/mm^3 and HIV RNA suppressed for 2 years, CD4 cell count measurement is optional.[30]

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation

10.10. Appendix 10: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the table of contents. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 3 (26 March 2023)

Overall Rationale for the Amendment:

Revised the primary efficacy objectives to evaluate the noninferiority and superiority of VE in each age stratum separately.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Throughout	• Amended the primary and secondary efficacy and immunogenicity objectives and related analyses. • Minor clarifying details were updated throughout the document. • Additional detail was added regarding the end of ILI surveillance.	• Revisions to the primary efficacy analysis are associated with regulatory agency feedback • Revisions to the immunogenicity objectives are to align with response to regulatory agency CCI [redacted].	Substantial
1.1 Synopsis	Updated to reflect the equivalent revisions in the body of the protocol.	To ensure the language is consistent with the body of the protocol	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
3 Objectives, Endpoints, and Estimands	• Revised the primary efficacy objectives to evaluate the noninferiority and superiority of VE in each age stratum separately (for participants 18 through 64 and ≥65 years of age). • Moved immunogenicity objectives to the exploratory objectives section. • Updated the primary safety objective to "18 through 64 years of age and ≥65 years of age" from "≥18 years of age" to align with estimand language. • CCI [redacted].	• Revisions to the primary efficacy analysis are associated with regulatory agency feedback. • Revisions to the immunogenicity objectives are to align with response to regulatory agency CCI [redacted].	Substantial
4.1 Overall Design	• Updated language to clarify that analysis of the primary efficacy may be conducted in each age stratum independently and may occur at different times. • Increased the number of participants who may be enrolled in the southern hemisphere to 30,000 and added a sentence to clarify that the total number of participants who may be enrolled is up to approximately 66,200.	• Revisions to the primary efficacy analysis are associated with regulatory agency feedback. • Increased the number of participants to enable additional enrollment in the southern hemisphere if required.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
6.1 Study Intervention(s) Administered	Revised the "IMP or NIMP" and "Sourcing" rows of the Study Intervention(s) table to provide extra information on the sourcing of licensed QIV (active comparator).	To enable flexibility for provision of study intervention.	Nonsubstantial
8.2.1 Surveillance for Influenza	CCI [redacted]	To allow CCI [redacted] results to be obtained on a nonexploratory basis to tie in with additional exploratory endpoints added in the previous amendment.	Substantial
8.2.2 Immunogenicity Assessments	CCI [redacted]	Provides flexibility for a different assay type to be utilized.	Nonsubstantial
8.6.1 Specified Genetics	Added details to confirm that influenza strain sequencing of LCI may also be conducted from swab samples.	CCI [redacted]	Substantial
8.10.6 ILI Surveillance (All Participants)	Revised language in relation to initiating ILI visits while there are ongoing symptoms from a prior visit to reflect that it is not a requirement that any symptoms from a preceding ILI visit must be resolved before another ILI visit is triggered (if a participant reports new, worsening, or recurrent symptoms).	Previous language was too restrictive, revised language provides more flexibility for when ILI visits can be initiated.	Nonsubstantial
9.1.1 Efficacy	Revised the primary efficacy objectives to evaluate the noninferiority and superiority of VE in each age stratum separately	To reflect the corresponding revisions to the Objectives section	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
9.1.4 Multiplicity Adjustment	Updated to reflect the hypothesis testing for the amended primary efficacy objectives and the hierarchical manner in which the hypothesis testing related to these objectives will occur.	To reflect the corresponding revisions to the Objectives section.	Substantial
9.2 Analysis Sets	Evaluable efficacy population definition revised to include additional details.	To align to the SAP language.	Substantial
9.3.2 Primary Endpoint(s)/Estimand(s) Analysis	Updated to reflect the amended primary efficacy objectives and related analyses.	To reflect the corresponding revisions to the Objectives section	Substantial
9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis	Updated to reflect the amended secondary efficacy objectives and related analyses.	To reflect the corresponding revisions to the Objectives section	Substantial
9.3.4 Tertiary/Exploratory Endpoint(s)	Updated the tertiary/exploratory objectives and related analyses.	To reflect the corresponding revisions to the Objectives section	Substantial
9.5 Analysis Timing	Updated language to clarify that analysis of the efficacy, immunogenicity, and safety objectives may be conducted in each age stratum independently and may occur at different times.	To reflect the corresponding revisions to the Objectives section.	Substantial
9.6.1 Relative Vaccine Efficacy	Updated the power calculations by RVE and LCI cases.	To reflect the corresponding revisions to the Objectives section	Substantial
10.4 Appendix 4: Genetics	CCI [redacted]	Relates to an exploratory objective added in a previous amendment.	Substantial
10.10 Appendix 10: Protocol Amendment History	Relocated to the Summary of Changes table (from the previous amendment) to the appropriate appendix.	Version control.	Nonsubstantial

Amendment 2 (09 November 2022)

Overall Rationale for the Amendment:

Addition of a possible second influenza season in the study and to expand enrollment for the northern hemisphere 2022-2023 influenza season.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Throughout	Added clarifying terminology regarding enrollment in the northern and southern hemispheres.	Change in the study design to potentially expand enrollment to the southern hemisphere for the 2023 influenza season and to increase enrollment for the northern hemisphere 2022-2023 influenza season.	Substantial.
1.1 Synopsis	Made updates to reflect the equivalent revisions in the body of the protocol.	Change in the study design to potentially expand enrollment to the southern hemisphere for the 2023 influenza season and to increase enrollment for the northern hemisphere 2022-2023 influenza season.	Substantial.
1.3 Schedule of Activities	For participants not included in the immunogenicity subset only, added the option for Visit 4 to be conducted as a telehealth visit.	To lessen the burden on sites and participants and aid in obtaining follow-up information expeditiously.	Substantial.
2.2.5 Clinical Overview	Specified the dose level of qIRV by age stratum.	Availability of Phase 2 safety and immunogenicity data.	Substantial.
2.3.1 Risk Assessment	Revised the interval between receipt of any mRNA-platform SARS-CoV-2 vaccine and study vaccination from 28 days to 14 days.	To correct a typographical error from the previous version of the protocol and to align with other sections.	Nonsubstantial.
3 Objectives, Endpoints, and Estimands	Revised endpoints of secondary immunogenicity objectives and added a new secondary objective. Removed an exploratory objective and added 2 new exploratory objectives.	Change in the study design to potentially expand enrollment to the southern hemisphere for the 2023 influenza season.	Substantial.
4.1 Overall Design	Revised to expand enrollment in the northern hemisphere by 11,200 participants across both age strata, increasing total enrollment to 36,200	Change in the study design to potentially expand enrollment to the southern hemisphere for the 2023 influenza season and to increase enrollment for the	Substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	CCI [redacted] for >65 and CCI [redacted] for 18 through 64 years of age). Added the ability to expand to the southern hemisphere.	northern hemisphere 2022-2023 influenza season.	
4.1 Overall Design	Specified the dose level of qIRV by age stratum.	Availability of Phase 2 safety and immunogenicity data.	Substantial.
4.3 Justification for Dose	Specified the dose level of qIRV by age stratum.	Availability of Phase 2 safety and immunogenicity data.	Substantial.
5.1 Inclusion Criteria	Revised inclusion criterion 1 to clarify that the minimum age of consent must be in accordance with local regulations.	To align with the internal protocol template.	Substantial.
5.2 Exclusion Criteria	Revised exclusion criterion 8 to include ongoing receipt of chronic antiviral therapy with activity against influenza.	To avoid compromising assessment of immunogenicity.	Substantial.
5.2 Exclusion Criteria	Added clarifying text to exclusion criterion 10 that study interventions may include additional procedures, such as collection of biological samples.	To avoid enrollment of participants in this study who are already enrolled in another study wherein procedures, such as respiratory illness visits, may interfere with compliance with this study's protocol.	Substantial.
6.1 Study Intervention(s) Administered	Included information pertaining to targeted influenza strains.	To clarify that vaccine strains of both qIRV (IMP) and QIV (NIMP) will differ between influenza seasons.	Substantial.
6.1 Study Intervention(s) Administered	Specified the dose level of qIRV by age stratum.	Availability of Phase 2 safety and immunogenicity data.	Substantial.
7.1 Discontinuation of Study Intervention	Clarified that participants who remain in the study for safety evaluation but refuse further study procedures should be contacted at both the 1-month and 6-month postvaccination time points.	Facilitate the collection of key safety data.	Substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
8.1.1 Telehealth Visits	For participants not included in the immunogenicity subset only, added the option for Visit 4 to be conducted as a telehealth visit.	To lessen the burden on sites and participants and aid in obtaining follow-up information expeditiously.	Substantial.
8.3.4 Reactogenicity Electronic Diary (Reactogenicity Subset Participants Only)	Added that participants not in the reactogenicity subset will have local reactions and systemic events detected and reported as AEs.	For clarity.	Substantial.
8.3.4.1 Grading Scales	Added that Grade 4 reactions must be entered on the participant's AE log and be evaluated for SAE reporting.	For clarity.	Substantial.
8.10.2 Visit 1 – Vaccination (Day 1)	Made clear which Visit 1 procedures must be conducted on the day of and prior to study intervention administration.	Clarifies the procedures that must be conducted on the day of and prior to study intervention administration following a temporary delay at Visit 1.	Substantial.
8.10.5 Visit 4 – 6-Month Follow-Up Visit (After Vaccination) – 175 to 189 Days After Visit 1	For participants not included in the immunogenicity subset only, added the option for Visit 4 to be conducted as a telehealth visit.	To lessen the burden on sites and participants and aid in obtaining follow-up information expeditiously.	Substantial.
8.10.6 ILI Surveillance (All Participants)	Added clarification that there is no minimum time between symptom start and/or resolution that would preclude an additional ILI visit.	For clarity.	Substantial.
9.1.4 Multiplicity Adjustment	Clarified that only immunogenicity data collected from C [redacted] CI [redacted] will be used for the immunogenicity noninferiority objective and superiority objective.	For clarity following change in the study design.	Substantial.
9.3.2 Primary Endpoint(s)/Estimand(s) Analysis	Made updates to the immunogenicity objective and related analysis.	Change in the study design to potentially expand enrollment to the southern hemisphere for the 2023 influenza season.	Substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis	Made updates to the secondary immunogenicity objectives, and added a secondary efficacy objective and related analysis.	Change in the study design to potentially expand enrollment to the southern hemisphere for the 2023 influenza season.	Substantial.
9.3.4 Tertiary/Exploratory Endpoint(s)	Made updates to tertiary/exploratory objectives and related analysis.	Change in the study design to potentially expand enrollment to the southern hemisphere for the 2023 influenza season.	Substantial.
9.3.5 Other Safety Analyses	Corrected the window for reporting symptoms that might be indicative of myocarditis or pericarditis or an AESI from 4 weeks to 14 days after study vaccination.	Align with additional procedures for monitoring of potential myocarditis or pericarditis detailed in Section 8.10.8.	Substantial.
9.5 Analysis Timing	Clarified timing of analysis.	Change in the study design to potentially expand enrollment to the southern hemisphere for the 2023 influenza season.	Substantial.
9.6.1 Relative Vaccine Efficacy	Made updates to reflect changes in sample size.	Change in the study design to potentially expand enrollment to the southern hemisphere for the 2023 influenza season and to increase enrollment for the northern hemisphere 2022-2023 influenza season.	Substantial.
9.6.3 Safety	Made updates to Table 6 to reflect changes in sample size.	Change in the study design to potentially expand enrollment to the southern hemisphere for the 2023 influenza season and to increase enrollment for the northern hemisphere 2022-2023 influenza season.	Substantial.

Amendment 1 (28 July 2022)

Overall Rationale for the Amendment:

Change in the design to be powered to study efficacy in participants ≥18 years of age.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
1. Protocol Summary	Updates to reflect the equivalent revisions in the body of the protocol.	Change in the study design to be powered for efficacy.	Substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
2.1. Study Rationale	Update to the rationale to include efficacy.	Change in the study design to be powered for efficacy.	Substantial.
2.2.1. Influenza	Addition of disease burden information for individuals 18 through 64 years of age.	As age group may now be included in the development plan.	Nonsubstantial.
2.2.5. Clinical Overview	Update to the design of C4781001 to reflect the latest protocol amendment.	Update to Phase 1/2 design	Substantial
2.3.1. Risk Assessment	Update to the risk profile of QIV using the package insert information from the standard-dose rather than high-dose QIV, given the likely comparator to be used in this age group.	Likely change to the comparator.	Substantial.
3. Objectives, Endpoints, and Estimands	Addition of primary and secondary efficacy objectives. Corresponding updates to other objectives.	Change in the study design to be powered for efficacy.	Substantial.
4.1. Study Design	Change in the design to be powered to study efficacy in participants ≥18 years of age, including update in the number of participants.	Change in the study design to be powered for efficacy.	Substantial.
4.3. Justification for Dose	Revised language pertaining to dose levels.	For clarity.	Substantial.
4.4. End of Study Definition	Revised to reflect the revised design.	Change in the study design to be powered for efficacy.	Substantial.
5.1. Inclusion Criteria	Removal of inclusion criterion 4.	To align with the internal protocol template.	Substantial.
5.2. Exclusion Criteria	Update to exclusion criterion 9 to decrease the window in which a modRNA-platform SARS-CoV-2 vaccine may be administered.	To aid enrollment without compromising participants' safety or compromising assessment of immunogenicity.	Substantial.
5.2. Exclusion Criteria	Update to exclusion criterion 10.	For clarity.	Substantial.
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention	Decrease in the window in which nonstudy vaccinations may be administered relative to study intervention.	To aid enrollment without compromising participants' safety or compromising assessment of immunogenicity.	Substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
6.1. Study Intervention(s) Administered	Removal of the unit dose strength; no change to study interventions.	To allow flexibility based on Phase 1/2 data.	Substantial.
6.9.1. Prohibited During the Study	Decrease in the window in which nonstudy vaccinations may be administered relative to study intervention.	To aid enrollment without compromising participants' safety or compromising assessment of immunogenicity.	Substantial.
8.1. Administrative Procedures and 8.2.2. Immunogenicity Assessments	Add clarification that blood draws will be taken from participants in the immunogenicity subset.	Consistent with the revised study design.	Substantial.
8.3. Safety Assessments and 8.3.4. Reactogenicity Electronic Diary	Add clarification that reactogenicity e-diaries will be used only in the reactogenicity subset.	Consistent with the revised study design.	Substantial.
8.3.5. Pregnancy Testing	Addition of this section and the requirement for all WOCBP to have a pregnancy test prior to vaccination.	Change in age group for the study.	Substantial.
8.4.1. Time Period and Frequency for Collecting AE and SAE Information	Updates to ensure consistency with Section 8.4.7.	Correct internal inconsistency in the document.	Substantial
8.10.2. Visit 1 – Vaccination (Day 1) and 8.10.4. Visit 3 – 4-Week Follow-Up Visit and 8.10.5. Visit 4 – 6-Month Follow-Up Visit (After Vaccination) – 175 to 189 Days After Visit 1	Add clarification that blood draws will be taken from participants in the immunogenicity subset.	Consistent with the revised study design.	Substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
8.10.2. Visit 1 – Vaccination (Day 1) and 8.10.3. Visit 2 – 1-Week Follow-Up Visit (After Vaccination) and 8.10.4. Visit 3 – 4-Week Follow-Up Visit and 8.10.5. Visit 4 – 6-Month Follow-Up Visit (After Vaccination) – 175 to 189 Days After Visit 1 and 8.10.7. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction	Add clarification where necessary that procedures relating to the reactogenicity e-diary apply only to those in the reactogenicity subset.	Consistent with the revised study design.	Substantial.
8.10.8. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis	Revised procedures for monitoring of potential myocarditis or pericarditis (changes to symptom[s] window after vaccination and cardiologist evaluation).	To lessen the burden on sites and aid in obtaining follow-up information expeditiously.	Substantial.
9.1. Statistical Hypotheses and 9.1.4. Multiplicity Adjustment	Updates to reflect a revised flexible hypothesis-testing approach.	Consistent with the revised study design.	Substantial.
9.1.3.1. Primary Estimands/Coprimary Estimands and 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis	Addition of a primary efficacy objective and related analysis.	Change in the study design to be powered for efficacy.	Substantial.
9.5. Analysis Timing	Updates to reflect alternative analysis timings based on whether a sufficient number of primary efficacy endpoint cases are accrued within the influenza season.	Change in the study design to be powered for efficacy.	Substantial.
9.6.1. Relative Vaccine Efficacy	Addition of this section to describe analyses to evaluate efficacy.	Change in the study design to be powered for efficacy.	Substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
9.6.2. Immunogenicity	Revised language to reflect the update in the study design such that all blood samples drawn will be assayed.	To reflect the revised study design.	Substantial.
9.6.3. Safety	Revised numbers provided in Table 6 to reflect the updated sample size.	To reflect the revised study design.	Substantial.
10.3.1. Male Participant Reproductive Inclusion Criteria	Revised text to include vasectomy, with the absence of sperm having been confirmed, as an allowable form of contraception for male participants.	Change in age group for the study.	Substantial.
10.3.2. Female Participant Reproductive Inclusion Criteria	Add a requirement for WOCBP to use contraception.	Change in age group for the study.	Substantial.

10.11. Appendix 11: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
BCR	breakpoint cluster region
bIRV	bivalent influenza modRNA vaccine
BLQ	below the limit of quantitation
BNT162b2	Pfizer's COVID-19 vaccine
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CCI	culture-confirmed influenza
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTIS	Clinical Trial Information System
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding

Abbreviation	Term
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eSAE	electronic safety adverse event
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition assay
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
ILI	influenza-like illness
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	institutional review board
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
KDIGO	Kidney Disease Improving Global Outcomes

Abbreviation	Term
LAIV	live attenuated influenza vaccine
LBBB	left bundle branch block
LCI	laboratory-confirmed influenza
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MCAR	missing completely at random
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
mIRV	monovalent influenza modRNA vaccine
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
mRNA	messenger ribonucleic acid
NA	neuraminidase
N/A	not applicable
NI	noninferiority
NIMP	noninvestigational medicinal product
CCI	[redacted]
PFS	prefilled syringe(s)
PI	principal investigator
PPE	personal protective equipment
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QTcF	QT interval corrected by the Fridericia formula
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
RVE	relative vaccine efficacy
SAE	serious adverse event
SADE	serious adverse device effect
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities

Abbreviation	Term
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
T bili	total bilirubin
TCR	T-cell receptor
UADE	unanticipated (serious) adverse device effect
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States package insert
VE	vaccine efficacy
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

11. REFERENCES

1 Cunha BA. Influenza: historical aspects of epidemics and pandemics. Infect Dis Clin North Am. 2004;18(1):141-55.

2 Monto AS, Gravenstein S, Elliott M, et al. Clinical signs and symptoms predicting influenza infection. Arch Intern Med. 2000;160(21):3243-7.

3 Cowling BJ, Chan KH, Fang VJ, et al. Comparative epidemiology of pandemic and seasonal influenza A in households. N Engl J Med. 2010;362(23):2175-84.

4 Hall E. Influenza. Chapter 12. In: Centers for Disease Control and Prevention. Hall E, Wodi AP, Hamborsky J, et al, eds. Epidemiology and prevention of vaccine-preventable diseases. 14th ed. Washington, DC: Public Health Foundation; 2021:179-92.

5 Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet. 2018;391(10127):1285-300.

6 Centers for Disease Control and Prevention. Estimated flu-related illnesses, medical visits, hospitalizations, and deaths in the United States — 2019–2020 flu season. Available from: https://www.cdc.gov/flu/about/burden/2019-2020.html. Accessed: 30 Jun 2022.

7 Centers for Disease Control and Prevention. Flu vaccination coverage, United States, 2020–21 influenza season. Available from: https://www.cdc.gov/flu/fluvaxview/coverage-2021estimates.htm#:~:text=Overall%2C%20among%20adults%20%E2%89%A518,(48.4%25%3B%20Figure%204). Accessed: 30 Jun 2022.

8 Cox NJ, Subbarao K. Influenza. Lancet. 1999;354(9186):1277-82.

9 Francis T Jr, Salk JE, Brace WM. The protective effect of vaccination against epidemic influenza B. JAMA. 1946;131:275-8.

10 Grohskopf LA, Sokolow LZ, Olsen SJ, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices, United States, 2015-16 influenza season. MMWR Morb Mortal Wkly Rep. 2015;64(30):818-25.

11 Frey S, Vesikari T, Szymczakiewicz-Multanowska A, et al. Clinical efficacy of cell culture-derived and egg-derived inactivated subunit influenza vaccines in healthy adults. Clin Infect Dis. 2010;51(9):997-1004.

[12] Belshe RB. The need for quadrivalent vaccine against seasonal influenza. Vaccine. 2010;28(Suppl 4):D45-53.

[13] Bresee JS, Fry AM, Sambhara S, et al. Inactivated influenza vaccines. Chapter 31. In: Plotkin S, Orenstein WA, Offit PA, eds. Plotkin's vaccines. 7th ed. Philadelphia, PA: Elsevier; 2018:456-88.e21.

[14] Co MDT, Orphin L, Cruz J, et al. In vitro evidence that commercial influenza vaccines are not similar in their ability to activate human T cell responses. Vaccine. 2009;27(2):319-27.

[15] European Medicines Agency. Influenza vaccines - non-clinical and clinical module. Available from: https://www.ema.europa.eu/en/influenza-vaccines-non-clinical-clinical-module. Published: 21 Jul 2016. Accessed: 05 May 2021.

[16] US Food and Drug Administration. Guidance for industry: clinical data needed to support the licensure of seasonal inactivated influenza vaccines. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-data-needed-support-licensure-seasonal-inactivated-influenza-vaccines. Published: May 2007. Accessed: 21 May 2021.

[17] Pardi N, Hogan MJ, Porter FW, et al. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov. 2018;17(4):261-79.

[18] Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603-15.

[19] Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. N Engl J Med. 2020;383(20):1920-31.

[20] Mulligan MJ, Lyke KE, Kitchin N, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586(7830):589-93.

[21] Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403-16.

[22] Centers for Disease Control and Prevention. Safety of COVID-19 vaccines. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/safety-of-vaccines.html. Updated: 16 May 2021. Accessed: 23 May 2022.

[23] CDC COVID-19 Response Team, Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine—United States, December 14–23, 2020. MMWR Morb Mortal Wkly Rep. 2021;70(2):46-51.

[24] European Medicines Agency. Summary of product characteristics for Comirnaty. Available from: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf. Updated: 24 Mar 2023. Accessed: 12 Jun 2023.

[25] Sahin U, Muik A, Vogler I, et al. BNT162b2 induces SARS-CoV-2-neutralising antibodies and T cells in humans. medRxiv. Available from: https://www.medrxiv.org/content/10.1101/2020.12.09.20245175v1. Accessed: 04 May 2021.

[26] US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

[27] Shimabukuro T. COVID-19 vaccine safety update. Advisory Committee on Immunization Practices. Published: 27 Jan 2021. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf. Accessed: 27 May 2022.

[28] Fluzone Standard-Dose [package insert]. Swiftwater, PA: Sanofi Pasteur Inc; 2022. Available from: https://www.fda.gov/media/119856/download. Accessed: 21 Jul 2022.

[29] Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737-49.

[30] Thompson MA, Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2021;73(11):e3572-605.

Document Approval Record

Document Name:	C4781004 Clinical Protocol Amendment 4 Clean Copy, 27 June 2023
Document Title:	A PHASE 3, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVA LUATE THE EFFICACY, SAFETY, TOLERABILITY, AND IMMUNOGE NICITY OF A MODIFIED RNA VACCINE AGAINST INFLUENZA COM PARED TO LICENSED INACTIVATED INFLUENZA VACCINE IN HE ALTHY ADULTS 18 YEARS OF AGE OR OLDER

Signed By:	Date(GMT)	Signing Capacity
PPD	27-Jun-2023 21:44:58	Final Approval
PPD	28-Jun-2023 12:29:17	Business Line Approver