A STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MODIFIED RNA VACCINES AGAINST INFLUENZA IN HEALTHY ADULTS

Study Intervention Number:	PF-07252220
Study Intervention Name:	Influenza modRNA vaccine
US IND Number:	30581
EudraCT Number:	N/A
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4781013
Phase:	1/2
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title:

A Study to Learn About Modified RNA Vaccines Against Influenza in Healthy Adults

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Document History

Document	Version Date
Amendment 1	26 April 2024
Original protocol	12 March 2024

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 1 (26 April 2024)

Overall Rationale for the Amendment:

- Addition of an exclusion criterion and stopping rule for Substudy A and Substudy B.
- Incorporating changes from a recently released PACL

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Updated the IND number to 30581.	To add the updated IND number (30581).	Protocol title page, Section 1.1 Synopsis.
Added an exclusion criterion to Substudy A and Substudy B for participants with prior history of myocarditis/pericarditis.	To allow the analysis of emergent safety data without confounding due to events in medical history.	Section 1.1 Synopsis, Section 10.11.5.2 Substudy A Exclusion Criteria, Section 10.12.5.2 Substudy B Exclusion Criteria.
Added a stopping rule for Substudy A and Substudy B.	To allow for the review of safety data ensuring participant safety.	Section 1.1 Synopsis, Section 2.7.1 Risk Assessment, Section 8.3.6 Stopping Rules. Addition of Section 10.11.8.3.1 Stopping Rules for Substudy A and Section 10.12.8.3.1 Stopping Rules for Substudy B.

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Description of Change	Brief Rationale	Section # and Name
Updated the collection period for confirmed diagnosis of the AESIs myocarditis and pericarditis from "within 14 days after vaccination" to "within 28 days after vaccination."	To allow for the review of safety data ensuring participant safety.	Section 8.4.8 Adverse Events of Special Interest.
Updated the monitoring period for potential myocarditis or pericarditis from "within 14 days after study intervention administration" to "within 28 days after study intervention administration."	To allow for the review of safety data ensuring participant safety.	Section 10.11.8.10.5. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis, Section 10.12.8.10.5. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis, Section 10.13.8.10.7. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis, Section 10.11.9.3.5. Other Analyses, Section 10.12.9.3.5. Other Analyses, Section 10.13.9.3.4. Other Analyses
Non-Substantial Modification(s)		
Added phrase "in Substudy C" to the following text in the second bullet point: "The stopping rule will pause randomization and study intervention administration at all dose levels in all groups in Substudy C."	To clarify that if a stopping rule is met, dosing will stop only in this specific substudy.	Section 10.13.8.3.1. Stopping Rules for Substudy C.
Removed "Grade 3" from the following text:	To correct a transcription error.	Section 10.11.8.10.4 Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction.

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Description of Change	Brief Rationale	Section # and Name
"If a suspected Grade 4 local reaction (Section 8.3.4.2), Grade 3 systemic event (Section 8.3.4.3), or fever ≥39.0°C (≥102.1°F) (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."		This clarification was also included in the PACL dated 16 Apr 2024.
Removed "days" from the following text in Inclusion criterion #3: "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 days before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.10."	To correct a transcription error.	Section 10.13.5.1 Substudy C Inclusion Criteria. This clarification was also included in the PACL dated 16 Apr 2024.
Removed ", if received" from the following text in the second bullet point: "Last dose of licensed influenza vaccine, if received."	Removed phrase as all participants in Substudy C are required to have received a 2023-2024 influenza vaccine at least 6 months prior to enrollment.	Section 10.13.6.9 Prior and Concomitant Therapy. This clarification was also included in the PACL dated 16 Apr 2024.

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Description of Change	Brief Rationale	Section # and Name
Updated the endpoint and estimand descriptions for the objective CCI [redacted]	The endpoint and estimand descriptions were not entered correctly in the original protocol.	Section 10.13.3 Objectives, Endpoints, and Estimands (Substudy C).
Updated "fever >39.0°C (>102.1°F)" to "fever >40.0°C (>104.0°F)" in the following text: "If a suspected Grade 4 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever >39.0°C (>102.1°F) (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."	To correct a transcription error.	Section 10.11.8.10.4 Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction, Section 10.12.8.10.4 Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction, Section 10.13.8.10.6 Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction.
Added "for Substudy C" in the section header. Added "in Substudy C" to the following sentence: "The following stopping rules are in place for all participants receiving tIRV or qIRV based on review of AEs and e-diary reactogenicity." Added "in Substudy C" to the second bullet point: "The stopping rule will pause randomization and study	To clarify that the stopping rules in this section apply to Substudy C only.	Section 10.13.8.3.1. Stopping Rules for Substudy C.

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Description of Change	Brief Rationale	Section # and Name
intervention administration at all dose levels in all groups."		
Removed "within 28 days" in the second bullet: If any participant vaccinated with tIRV or qIRV dies within 28 days following administration of study intervention, irrespective of investigator assessment of relatedness.	To remove duplicative language in the stopping rules section.	Section 10.13.8.3.1. Stopping Rules for Substudy C.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Study to Evaluate the Safety, Tolerability, and Immunogenicity of Modified RNA Vaccines Against Influenza in Healthy Adults

Brief Title:

A Study to Learn About Modified RNA Vaccines Against Influenza in Healthy Adults

Regulatory Agency Identification Number(s):

US IND Number:	30581
EudraCT Number:	N/A
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4781013
Phase:	1/2

Rationale:

The World Health Organization (WHO) recommendation for the composition of influenza virus vaccines in the 2023-2024 northern hemisphere influenza season includes both a quadrivalent and a trivalent vaccine, differing by the presence/absence of the B/Yamagata lineage, considering that the B/Yamagata lineage has not been seen in circulation since March 2020. At the 05 October 2023 Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting, the committee recommended to move to trivalent influenza vaccines excluding the B/Yamagata lineage from strain compositions. Thus, this study will mainly assess trivalent nucleoside-modified messenger ribonucleic acid (modRNA) vaccine formulations targeting 2 influenza A virus types (H1N1 and H3N2) and 1 influenza B virus (B/Victoria lineage).

Pfizer is currently developing a messenger ribonucleic acid (mRNA)-based influenza vaccine, which has been administered to younger (18 through 64 years of age) and older (≥65 years of age) adults in several clinical studies, as described in the investigator's brochure (IB). Immunogenicity data from these studies suggest that influenza A strain hemagglutination inhibition assay (HAI) and cell-mediated (both CD4 and CD8) responses are comparable to or better than those observed following vaccination with a licensed influenza vaccine, though the influenza B HAI responses following vaccination with quadrivalent influenza modRNA vaccine (qIRV) are somewhat attenuated.

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The purpose of Substudies A and B is to evaluate the safety and immunogenicity of additional influenza modRNA vaccine candidates optimized to enhance immunogenicity against influenza B viruses while maintaining or enhancing vaccine-induced immunogenicity against influenza A viruses. Substudy C will assess the safety CCI of a quadrivalent modRNA vaccine targeting CCI in older adults (≥65 years of age).

CCI

Substudy C will explore the CCI safety of vaccines containing CCI

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Objectives, Endpoints, and Estimands:

[redacted] **objectives are detailed in the protocol.**

Substudy A

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To define the safety and tolerability profile of trivalent influenza modRNA vaccines (tIRVs) in participants 18 through 64 years of age	• 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) • Adverse events (AEs) • Serious adverse events (SAEs) • Medically attended adverse events (MAEs) • Newly diagnosed chronic medical conditions (NDCMCs)	In participants receiving study intervention (safety population), the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs through 4 weeks after vaccination • MAEs through 6 months after vaccination • NDCMCs through 6 months after vaccination • SAEs through 6 months after vaccination
Secondary:	**Secondary:**	**Secondary:**
• To describe the immune response elicited by tIRVs in participants 18 through 64 years of age	• HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for [redacted] influenza vaccines	In participants complying with the key protocol criteria (evaluable immunogenicity population [HAI [redacted]]): • HAI geometric mean titers (GMTs) at baseline and 4 weeks after vaccination • HAI geometric mean fold rises (GMFRs) from before vaccination to 4 weeks after vaccination • The proportion of participants achieving HAI seroconversion[a] 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

a. 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 at least a 4-fold rise at the time point of interest.

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Substudy B

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To define the safety and tolerability profile of tIRVs in participants ≥65 years of age	• 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 • MAEs • NDCMCs	In participants receiving study intervention (safety population), the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs through 4 weeks after vaccination • MAEs through 6 months after vaccination • NDCMCs through 6 months after vaccination • SAEs through 6 months after vaccination
Secondary:	**Secondary:**	**Secondary:**
• To describe the immune response elicited by tIRVs in participants ≥65 years of age	• HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI influenza vaccines	In participants complying with the key protocol criteria (evaluable immunogenicity population [HAI CCI]): • HAI GMTs at baseline and 4 weeks after vaccination • HAI GMFRs from before vaccination to 4 weeks after vaccination • The proportion of participants achieving HAI seroconversion[a] 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

a. 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 at least a 4-fold rise at the time point of interest.

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Substudy C

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To define the safety and tolerability profile of tIRVs and qIRV in participants ≥65 years of age	• 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 • MAEs • NDCMCs	In participants receiving study intervention (safety population), the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs through 4 weeks after vaccination • MAEs through 6 months after vaccination • NDCMCs through 6 months after vaccination • SAEs through 6 months after vaccination

Overall Design:

Substudies detailed in this protocol will be conducted independently from each other and therefore enrollment into each may occur concurrently or at separate times.

Substudy A

This is a Phase 2, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, and immunogenicity of 3 different formulations of tIRV (tIRV1 through tIRV3) encoding HA for the targeted seasonal influenza strains compared to quadrivalent influenza vaccine 1 (QIV1) (CCI and qIRV (encoding HA for 2 A and 2 B seasonal influenza strains) in healthy adults 18 through 64 years of age.

Up to approximately 450 participants 18 through 64 years of age will be enrolled and randomized to receive 1 dose of study intervention as shown in the table below. Depending on the availability of study intervention and operational prioritization, study intervention groups may not all be randomized concurrently; however, a minimum of 2 groups will be open for randomization at any one time.

Number of Participants to Be Enrolled in Substudy A – Participants 18 Through 64 Years of Age

Study Intervention Group	Study Intervention	Preformulated[a]	Total modRNA Dose	Number of Participants
1A	QIV1	Yes	N/A	90
2A	tIRV1	Yes	CCI	90
3A	tIRV2	No		90
4A	tIRV3	No		90
5A	qIRV1	Yes		90

a. For tIRV2 and tIRV3 (which are not preformulated), monovalent influenza modRNA vaccines (mIRVs) encoding HA for each A and B strain will be mixed at the site to generate these study interventions at the dose-level combination shown. Please see the investigational product manual (IPM) for further details.

Blood samples of approximately 30 mL will be collected CCI prior to vaccination and at 4 weeks and 6 months after vaccination.

Local reaction and systemic event data will be collected in an electronic diary (e-diary) during the 7-day follow-up period, or longer for ongoing symptoms, after study vaccination (ie, from Day 1, the day of vaccination, until event resolution).

All AEs will be collected from informed consent signing through 4 weeks following vaccination. A subset of AEs (NDCMCs, MAEs, 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 will be collected.

Stopping rules will apply as detailed in the protocol.

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Substudy B

This is a Phase 2, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, and immunogenicity of 2 different formulations of tIRV (tIRV2 and tIRV3) encoding HA for the targeted seasonal influenza strains compared to QIVs ([CCI]) and qIRV2 (encoding HA for 2 A and 2 B seasonal influenza strains) in healthy adults ≥65 years of age.

Up to approximately 450 participants ≥65 years of age will be enrolled and randomized to receive 1 dose of study intervention as shown in the table below. Depending on the availability of study intervention and operational prioritization, study intervention groups may not all be randomized concurrently; however, a minimum of 2 groups will be open for randomization at any one time.

Number of Participants to Be Enrolled in Substudy B – Participants ≥65 Years of Age

Study Intervention Group	Study Intervention	Preformulated[a]	Total modRNA Dose	Number of Participants
1B	QIV2	Yes	N/A	90
2B	QIV3	Yes	N/A	90
3B	tIRV2	No	[CCI]	90
4B	tIRV3	No		90
5B	qIRV2	Yes		90

a. For tIRV2 and tIRV3 (which are not preformulated), mIRVs encoding HA for each A and B strain will be mixed at the site to generate these study interventions at the dose-level combination shown. Please see the IPM for further details.

Blood samples of approximately 30 mL will be collected [CCI] prior to vaccination and at 4 weeks and 6 months after vaccination.

Local reaction and systemic event data will be collected in an e-diary during the 7-day follow-up period, or longer for ongoing symptoms, after study vaccination (ie, from Day 1, the day of vaccination, until event resolution).

AEs will be collected from informed consent signing through 4 weeks following vaccination; NDCMCs, MAEs, 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 will be collected.

Stopping rules will apply as detailed in the protocol.

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Substudy C

This is a Phase 1, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, CCI of various formulations of tIRV (encoding HA CCI for the targeted seasonal strains [tIRV3 through tIRV8]) and qIRV3 CCI compared to QIVs CCI in healthy adults ≥65 years of age.

Up to approximately 270 participants ≥65 years of age will be enrolled and randomized to receive 1 dose of study intervention as shown in the table below. Depending on the availability of study intervention and operational prioritization, study intervention groups may not all be randomized concurrently; however, a minimum of 2 groups will be open for randomization at any one time.

Number of Participants to Be Enrolled in Substudy C – Participants ≥65 Years of Age

Study Intervention Group	Study Intervention	Preformulated	CCI	CCI	Total modRNA Dose	Number of Participants
1C	QIV2	Yes	N/A		N/A	30
2C	QIV3	Yes	N/A		N/A	30
3C	tIRV3	No	Yes		CCI	30
4C	tIRV4	No	Yes			30
5C	qIRV3	No	Yes			30
6C	tIRV5	No	Yes			30
7C	tIRV6	No	Yes			30
8C	tIRV7	No	Yes			30
9C	tIRV8	No	Yes			30

Study intervention groups in which participants receive QIV2, QIV3, or modRNA doses up to CCI will initially be enrolled as detailed in the protocol. Safety data accumulated at least 7 days following vaccination of at least 20 participants in these groups will be reviewed by the sponsor and, if it is deemed acceptable, participants will be enrolled into study intervention groups in which they will receive modRNA doses up to CCI

For all study intervention groups:

- Enrollment will be controlled such that no more than 10 participants per group can be vaccinated on the first day. Safety data accumulated at least 72 hours after 10 participants have received study intervention in each group will be reviewed by the sponsor and vaccination of the remaining participants in each group will commence in a staggered manner if these data raise no safety concerns as shown in the protocol.

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- Stopping rules will apply as detailed in the protocol.

Blood samples of approximately 30 mL will be collected CCI prior to vaccination and at 4 weeks and 6 months after vaccination. Additional blood samples will be collected as summarized below:

- Approximately CCI mL of blood will be collected from participants (approximately 20 participants per group) who consent to this at the time points specified in the protocol CCI

- Approximately 2.5 mL of blood will be collected from all participants at screening for assessment of troponin I.

Local reaction and systemic event data will be collected in an e-diary during the 7-day follow-up period, or longer for ongoing symptoms, after study vaccination (ie, from Day 1, the day of vaccination, until event resolution).

All AEs will be collected from informed consent signing through 4 weeks following vaccination. A subset of AEs (NDCMCs, MAEs, 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 will be collected.

Number of Participants:

Up to approximately 450 participants will be enrolled in Substudy A, up to approximately 450 participants in Substudy B, and up to approximately 270 participants in Substudy C.

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

Study Population:

Please refer to the protocol for a full list of eligibility criteria.

Key Inclusion Criteria – Substudies A and B

- Participants 18 through 64 years of age (Substudy A) or ≥65 years of age (Substudy B) on Day 1.

- 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.

Key Inclusion Criteria – Substudy C

- Participants ≥65 years of age on Day 1.

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- 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.

- Receipt of licensed influenza vaccination for the 2023-2024 northern hemisphere season ≥6 months (≥180 days) before study intervention administration.

Key Exclusion Criteria – Substudies A and B

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

- Diagnosed with influenza by a Food and Drug Administration (FDA)-approved testing method ≤180 days before study intervention administration.

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

- Prior history of myocarditis or pericarditis.

- Any participant who has received investigational or licensed influenza vaccination within 6 months (180 days) before study intervention administration.

Key Exclusion Criteria – Substudy C

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

- Diagnosed with influenza by an FDA-approved testing method ≤180 days before study intervention administration.

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

- Prior history of heart disease of concern: history of myocarditis, pericarditis, cardiomyopathy, coronary artery disease (including history of myocardial infarction, unstable angina), New York Heart Association (NYHA) Class III and above heart failure, or significant arrhythmias.

  Note: Controlled hypertension is not exclusionary. “Controlled” is defined as hypertension not requiring significant change in therapy or hospitalization for worsening hypertension during the 6 weeks before enrollment.

- Abnormal troponin I value at screening.

- Screening 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results, as judged by the investigator, and/or is consistent with probable or possible myocarditis or pericarditis.

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Study Arms and Duration:

In each substudy, participants will receive 1 dose of study intervention on Day 1. Please see the Overall Design section above for study intervention groups/study arm details.

Statistical Methods:

The following summarizes the statistical methods for all substudies (A, B, and C).

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

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

The immunogenicity objectives will be summarized: HAI CCI [redacted] GMT, HAI CCI [redacted] GMFR, percentage of participants achieving seroconversion measured by HAI, and percentage of participants with HAI titer ≥1:40, at designated time points and using the associated 95% confidence interval (CI). CCI [redacted] for CCI [redacted] may be specified in the statistical analysis plan (SAP).

As the sponsor remains unblinded during study conduct, informal analyses of the data may be performed to inform future clinical development activities.

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 following vaccination, as well as enlarged lymph glands, pain (most frequently described as body aches), and nausea.
- The safety profile of a novel vaccine is not yet fully characterized, so the full extent of risks is unknown.
- Very rare cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of modRNA-based coronavirus disease 2019 (COVID-19) vaccine (BNT162b2).
- Venipuncture will be performed during the study. There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.
- Protection against onset of influenza disease cannot be confirmed for participants receiving investigational influenza vaccines.

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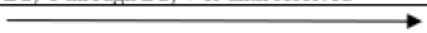
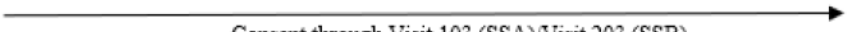
- As study participants are prohibited from receiving off-study influenza vaccine, this may impact timing of when a study participant may be vaccinated against seasonal influenza.
- Benefits to individual participants may be:
  - Contributing to research to help others.

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

1.2. Schema

1.2.1. Substudy A and Substudy B (Phase 2) Schema

SSA: Healthy Adults 18 Through 64 Years of Age **SSB:** Healthy Adults ≥65 Years of Age	**SSA: Visit 101** **SSB: Visit 201** (Day 1 - Vaccination)	**SSA: Visit 102** **SSB: Visit 202** (4-Week Follow-Up Visit)	**SSA: Visit 103** **SSB: Visit 203** (6-Month Follow-Up Visit)
Vaccination			
Blood Draw (CCI [redacted])			
SAFETY			
Local Reactions and Systemic Events	 Day 1 through Day 7 or until resolved		
AEs	 Consent through Visit 102 (SSA)/Visit 202 (SSB)	 48 Hours after blood draw	
MAEs, NDCMCs, and SAEs	 Consent through Visit 103 (SSA)/Visit 203 (SSB)		

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1.2.2. Substudy C (Phase 1) Schema

Healthy Adults ≥65 Years of Age	Screening	Visit 301 (Day 1 - Vaccination	Visit 302 (1-Week Follow-Up Visit)	Visit 303 (4-Week Follow-Up Visit)	Visit 304 (6-Month Follow-Up Visit)
Vaccination					
Blood Draw [redacted]					
Blood Draw ([redacted])					
Blood Draw (Troponin I)					
SAFETY					
Local Reactions and Systemic Events		Day 1 through Day 7 or until resolved			
AEs		Consent through Visit 303		48 Hours after blood draw	
MAEs, NDCMCs, and SAEs		Consent through Visit 304			

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.

See Section 10.11.1 for the Substudy A SoA.

See Section 10.12.1 for the Substudy B SoA.

See Section 10.13.1 for the Substudy C SoA.

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2. INTRODUCTION

2.1. Study Rationale

The WHO recommendation for the composition of influenza virus vaccines in the 2023-2024 northern hemisphere influenza season includes both a quadrivalent and a trivalent vaccine, differing by the presence/absence of the B/Yamagata lineage, considering that the B/Yamagata lineage has not been seen in circulation since March 2020.[1] At the 05 October 2023 VRBPAC meeting, the committee recommended to move to trivalent influenza vaccines excluding the B/Yamagata lineage from strain compositions.[2] Thus, this study will mainly assess trivalent modRNA vaccine formulations targeting 2 influenza A virus types (H1N1 and H3N2) and 1 influenza B virus (B/Victoria lineage).

Pfizer is currently developing an mRNA-based influenza vaccine, which has been administered to younger (18 through 64 years of age) and older (≥65 years of age) adults in several clinical studies, as described in the IB. Immunogenicity data from these studies suggest that influenza A strain HAI and cell-mediated (both CD4 and CD8) responses are comparable to or better than those observed following vaccination with a licensed influenza vaccine, though the influenza B HAI responses following vaccination with qIRV are somewhat attenuated. The purpose of Substudies A and B is to evaluate the safety and immunogenicity of additional influenza modRNA vaccine candidates optimized to enhance immunogenicity against influenza B viruses while maintaining or enhancing vaccine-induced immunogenicity against influenza A viruses.

Substudy C will assess the safety CCI of a quadrivalent modRNA vaccine targeting CCI in older adults (≥65 years of age). CCI , Substudy C will explore the CCI safety of vaccines containing CCI CCI

CCI

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These assessments will be conducted across 3 substudies:

- Substudy A: a Phase 2, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, and immunogenicity of 3 different formulations of tIRV encoding HA for the targeted seasonal strains compared to licensed influenza vaccines and qIRV1 (encoding HA for 2 A and 2 B seasonal strains) in healthy adults 18 through 64 years of age.

- Substudy B: a Phase 2, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, and immunogenicity of 2 different formulations of tIRV encoding HA for the targeted seasonal strains compared to licensed influenza vaccines and qIRV2 (encoding HA for 2 A and 2 B seasonal strains) in healthy adults ≥65 years of age.

- Substudy C: a Phase 1, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, CCI [redacted] of various formulations of tIRV (encoding HA CCI [redacted] for the targeted seasonal strains) and qIRV3 CCI [redacted] compared to CCI [redacted] in healthy adults ≥65 years of age.

2.2. Background

Influenza is a major cause of morbidity and mortality worldwide, occurring in annual seasonal epidemics and occasionally in global pandemics.[8] Symptomatic influenza infection causes a febrile illness with respiratory and systemic symptoms, although it may often be asymptomatic.[9,10] 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, while the annual global number of deaths is estimated to range from almost 300,000 to over 600,000.[11,12] In the US, the estimated influenza disease burden for the 2022-2023 season was 369,372 hospitalizations, with 129,263 accounted for by 18- through 64-year-olds and 192,087 by older adults ≥65 years of age. The same data estimated that the US annual mortality burden due to influenza among all ages was 21,401 deaths, with 5526 deaths occurring among 18- through 64-year-olds and 15,399 deaths in older adults ≥65 years of age.[13] The in-season estimates of influenza burden for the 2023-2024 US influenza season (from 01 October 2023 through 17 February 2024) are approximately 25 to 46 million influenza illnesses, 11 to 21 million influenza medical visits, 280,000 to 580,000 influenza hospitalizations, and 17,000 to 50,000 influenza deaths.[14] These estimates indicate that influenza remains a major public health challenge.

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2.3. Influenza Vaccination

The first influenza vaccines were licensed in the 1940s, and now a number of different types of licensed influenza vaccines exist: inactivated, recombinant, and LAIV.[15,16] The viruses that form the basis for inactivated vaccines are replicated in either embryonated hens' eggs or mammalian cell lines.[17] Some of the vaccines recommended for adults 65 years of age and older provide higher doses of influenza antigens and one is combined with an adjuvant, known as MF59, to improve the immune response, particularly important in older individuals.[16] Vaccines are produced for routine seasonal immunization, targeting 3 or 4 influenza viruses.[16] Trivalent vaccines target 2 A subtypes (H1N1, H3N2) and 1 B virus (B/Victoria lineage). As of the 2023-2024 northern hemisphere influenza season, these are currently no longer in commercial use in the US.[18] Quadrivalent vaccines, which target an additional B virus (B/Yamagata lineage) to cover 2 antigenically distinct lineages, are currently administered in the US.[18,19] Standard inactivated vaccines given to adults generally contain 15 µg of each HA for adult intramuscular injection, although the high-dose inactivated vaccine contains 60 µg of each HA.[20]

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.[20] This means that the schedule for vaccine production, release, and administration is highly compressed.

As development and administration of influenza vaccines requires stringent coordination between influenza strain surveillance and selection for vaccine use and manufacture of these vaccines prior to the onset of the next influenza season, having a rapidly responsive manufacturing platform capable of large doses of vaccine for administration offers significant value in the prevention of influenza. Given the rapid supply response for distribution of Comirnaty® during the COVID-19 pandemic, this supports the exploration of the modRNA platform for potentially rapid development of vaccines encoding the seasonal influenza strains for the prevention of influenza.

2.3.1. Assessing Influenza Vaccine Immunogenicity

Dependent upon the components included in each influenza vaccine, vaccination is intended to induce antibodies against HA [redacted][21] Strain-specific immunogenicity can be measured by the HAI, [redacted] antibody titers measured by the HAI are most commonly used to assess vaccine responses.[20] In general, an HAI titer between 1:32 and 1:40 is considered protective at a population level, which is thought to reduce the risk of onset of influenza in 50% to 70% of cases.[20,22] This is reflected in regulatory guidance, where, for example, seroconversion is defined as the percentage of participants with either 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.[20]

Regulatory guidance allows for authorization of a new seasonal influenza vaccine on the basis of immunogenicity and/or efficacy data.[22,23]

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2.4. Nucleoside-Modified mRNA Vaccines

Over the last several years, the use of mRNA as the basis for potential vaccine candidates has shown increasing promise.[24] 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.[24]

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).[25,26] ModRNA vaccine candidate dose levels up to 100 µg and 250 µg were studied in the candidate-selection/dose-finding stage of development for the 2 vaccines, respectively.[26,27] Phase 3 development was conducted with 2 doses of BNT162b2 30 µg for children 12 years of age and older and 2 doses of mRNA-1273 100 µg for adults 18 years of age and older, with both vaccines demonstrated to be highly effective with no identified significant safety concerns, and both have now received full approval for use in the US.[25,28,29,30,31]

2.5. 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, 1 to 2 B [redacted] for the prevention of influenza.

The modRNA platform would present a number of potential advantages. Manufacturing could be accelerated, as no reassortment 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) [redacted] could improve upon the efficacy observed with existing influenza vaccines.[7,32]

2.6. Clinical Overview

Pfizer is currently developing an mRNA-based influenza vaccine, and this vaccine has now been administered to younger (18 through 64 years of age) and older (≥65 years of age) adults in several clinical studies. For additional details, please refer to the influenza modRNA vaccine IB.

2.7. Benefit/Risk Assessment

The mRNA platform is well suited to potential use in the production of influenza vaccines. Based on its approach of directly encoding proteins that are associated with influenza strains causing disease, RNA influenza vaccines are a more precise match to the circulating seasonal influenza strains. With rapid, large-scale capability, there may be greater assurance of timely seasonal influenza supply as well as greater potential for rapid mobilization of vaccines in the event of a pandemic influenza outbreak. The ability of an RNA vaccine to rapidly scale and protect against an emerging viral strain has been demonstrated for a different virus: SARS-CoV-2. BNT162b2, which shares the same manufacturing method and LNP

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composition as the investigational influenza vaccines in this study, has exceeded 1 billion dose administrations globally since its initial emergency use authorization in the US in December 2020.[33] This significant vaccine use in a broad population provides a significant amount of information relating to the safety features of RNA vaccines.

This study will be evaluating RNA doses CCI [redacted] The safety profile of doses of mRNA encoding influenza antigens tested up to CCI in ongoing or completed clinical trials suggests a similar safety profile to that of BNT162b2. The key risks are shown in Section 2.7.1.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tIRVs and qIRVs may be found in the IB, which is the SRSD for this study.

The SRSD for the comparator agent QIV1 is the CCI [redacted] USPI.

The SRSD for the comparator agent QIV2 is the CCI [redacted] USPI.

The SRSD for the comparator agent QIV3 is the CCI [redacted] USPI.

Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

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2.7.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): tIRV and 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, as well as enlarged lymph glands, pain (most frequently described as body aches), and nausea.	These are common adverse reactions seen with other vaccines, 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.[25,34] 1-Week follow-up reactogenicity data of participants who received modRNA vaccines (mIRV, bIRV, or qIRV) in Study C4781001 for both Substudy A and 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.	All study participants will be observed at the study site for at least 30 minutes after vaccination. 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.
The safety profile of a novel vaccine is not yet fully characterized.	Certain tIRVs and qIRV3 are novel vaccines based on the same platform CCI [redacted] as qIRV, CCI [redacted] qIRV1 and qIRV2 CCI [redacted] were previously evaluated in Phase 1 and 2 studies, and the Phase 3 trial is ongoing. Although qIRV3, which is based on a modRNA platform, is a novel vaccine, available data from Phase 1/2 support an acceptable safety profile of modRNA-based vaccines. Furthermore, (1) marketed vaccines for influenza immunization using different manufacturing technology and (2) COVID-19 vaccines using the same mRNA technology have been shown to be safe and effective.	All AEs will be collected from the signing of the ICD through 4 weeks after vaccination and SAEs/MAEs/NDCMCs will be collected through 6 months after vaccination. All participants will be observed for at least 30 minutes after vaccination in addition to review of reactogenicity data.

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 COVID-19 vaccines.	Anaphylaxis: The estimated rate is 5.0 per million doses administered.[35] Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine, and within 14 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. Based on accumulating data, the reporting rates of myocarditis and pericarditis after the primary series in children 5 to <12 years of age are lower than in children 12 through 17 years of age. Postauthorization safety data surveillance has confirmed the safety profile observed in COVID-19 Study C4591001 and has resulted in identification of some additional adverse reactions (risks) as noted in the SRSD.	Specific reference to these risks for the COVID-19 vaccine is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. Receipt of any mRNA SARS-CoV-2 vaccine within 28 days before and 28 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 detailed for each substudy. Additionally, each substudy will incorporate stopping rule(s).
Limited data are available regarding the efficacy of the tIRV and qIRV candidates that will be assessed during this study, and participants are prohibited from receiving nonstudy influenza vaccines during the study.	There is a risk that participants may develop breakthrough influenza infection during the course of the study.	This study will primarily be conducted during the nonpeak period of influenza circulation in the US, and licensed activated influenza vaccines will be used in comparator study arms.

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Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): QIV1		
Local and systemic reactions to the vaccine may occur.	The following summary represents the CCI safety profile: In adults 18 through 64 years of age, the most commonly reported injection-site adverse reactions were pain (CCI), erythema (CCI%), and induration %). The most common systemic adverse reactions were headache CCI%), fatigue (CCI%), and myalgia (CCI%).[36]	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.
Study Intervention(s): QIV2		
Local and systemic reactions to the vaccine may occur.	The following summary represents the CCI safety profile: In adults ≥65 years of age, the most common injection-site reaction was pain (CCI%); the most common prompted systemic adverse events were myalgia (CCI%), headache (CCI%), and malaise CCI%).[37]	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.
Study Intervention(s): QIV3		
Local and systemic reactions to the vaccine may occur.	The following summary represents the CCI safety profile: In adults ≥65 years of age, the most common CCI%) local (injection site) adverse reaction was injection site pain CCI%); the most common CCI%) systemic adverse reactions were headache (CCI%) and fatigue CCI%).[38]	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.
Study Procedures		
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.

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2.7.2. Benefit Assessment

Benefits to individual participants may be:

- Contributing to research to help others.

2.7.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

See Section 10.11.3 for objectives, endpoints, and estimands for Substudy A.

See Section 10.12.3 for objectives, endpoints, and estimands for Substudy B.

See Section 10.13.3 for objectives, endpoints, and estimands for Substudy C.

4. STUDY DESIGN

4.1. Overall Design

Substudies detailed in this protocol will be conducted independently from each other and therefore enrollment may occur concurrently or at separate times.

See Section 10.11.4.1 for the overall design of Substudy A.

See Section 10.12.4.1 for the overall design of Substudy B.

See Section 10.13.4.1 for the overall design of Substudy C.

4.2. Scientific Rationale for Study Design

See Section 2.1.

4.2.1. Patient Input Into Design

There has not been direct patient involvement in the design of this protocol; however, Pfizer has a long history of enrolling participants in similarly designed safety, tolerability, and immunogenicity vaccine studies. The design of these studies has evolved over time to incorporate any feedback received. The acceptability of vaccine studies of this type to the intended participant population is demonstrated by low (typically ~5%) screen failure rates.

4.2.2. Diversity of Study Population

See Section 5.

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4.2.3. Rationale for Comparator

The use of licensed inactivated influenza vaccines as comparators is based on the CBER guidance, which supports approval of new seasonal influenza vaccines based on demonstration of noninferior immune responses elicited by candidate vaccines compared to US-licensed CCI influenza vaccines.[39] Several licensed seasonal influenza vaccines are available and recommended by the ACIP for use in the ≥18-year age group that will be enrolled in this study.[18] Therefore, licensed CCI influenza vaccines will be used as comparators in this study for both age groups. CCI

[redacted].[1,18]

4.2.4. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for tIRVs and qIRVs, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Section 10.4).

4.3. Justification for Dose

The ongoing and completed influenza modRNA vaccine studies (tIRV and qIRV) in adults ≥18 years of age have demonstrated an acceptable safety and tolerability profile of modRNA qIRV doses up to CCI

[redacted]

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CCI [redacted]

4.4. End of Study Definition

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

See Section 10.11.4.4 for the end of Substudy A definition.

See Section 10.12.4.4 for the end of Substudy B definition.

See Section 10.13.4.4 for the end of Substudy C definition.

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.

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

5.1. Inclusion Criteria

See Section 10.11.5.1 for the Substudy A inclusion criteria.

See Section 10.12.5.1 for the Substudy B inclusion criteria.

See Section 10.13.5.1 for the Substudy C inclusion criteria.

5.2. Exclusion Criteria

See Section 10.11.5.2 for the Substudy A exclusion criteria.

See Section 10.12.5.2 for the Substudy B exclusion criteria.

See Section 10.13.5.2 for the Substudy C exclusion criteria.

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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 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

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 randomized 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 failure) may be rescreened under a new participant number.

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

See Section 10.11.5.5 for Substudy A temporary delay criteria.

See Section 10.12.5.5 for Substudy B temporary delay criteria.

See Section 10.13.5.5 for Substudy C temporary delay criteria.

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.

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6.1. Study Intervention(s) Administered

See Section 10.11.6.1 for study interventions administered during Substudy A.

See Section 10.12.6.1 for study interventions administered during Substudy B.

See Section 10.13.6.1 for study interventions administered during Substudy C.

Table 1 describes the vaccine details for each of the constituent parts of the modRNA-containing study interventions.

Table 1. Substudy A, Substudy B, and Substudy C: Vaccine Details

Vaccine Preparation	Influenza Strains	CCI
PF-07966731, Influenza modRNA Suspension for Injection, 0.1 mg/mL	CCI	
PF-07871853, Influenza modRNA Suspension for Injection, 0.1 mg/mL		
PF-08010605, Influenza modRNA Suspension for Injection, 0.1 mg/mL		
PF-07872963, Influenza modRNA Suspension for Injection, 0.1 mg/mL		
PF-07973057, Quadrivalent Influenza modRNA Suspension for Injection, 0.06 mg/mL	2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI influenza vaccines CCI	
PF-07973057, Quadrivalent Influenza modRNA Suspension for Injection, 0.12 mg/mL	2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI influenza vaccines CCI	
PF-08011473, Trivalent Influenza modRNA Suspension for Injection, 0.09 mg/mL (CCI	2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI influenza vaccines CCI	
PF-07973257, Influenza mod RNA Suspension for Injection, 0.1 mg/mL	CCI	
PF-07872962, Influenza modRNA Suspension for Injection, 0.1 mg/mL		
PF-07872964, Influenza modRNA Suspension for Injection, 0.1 mg/mL		

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6.1.1. Administration

See Section 10.11.6.1.1 for study intervention administration details for Substudy A.

See Section 10.12.6.1.1 for study intervention administration details for Substudy B.

See Section 10.13.6.1.1 for study intervention administration details for Substudy C.

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 must be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions will 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

Comparator vaccines detailed in Section 10.11.6.1, Section 10.12.6.1, and Section 10.13.6.1 may be provided as a PFS and, in which case, should be considered a medical device.

1. Instructions for medical device use are provided in the USPI.

2. All medical device deficiencies (including malfunction, use error, and inadequate labeling) for the above-listed medical devices 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.

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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 storage conditions of the 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

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

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.

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

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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

See Section 10.11.6.4 for Substudy A blinding arrangements.

See Section 10.12.6.4 for Substudy B blinding arrangements.

See Section 10.13.6.4 for Substudy C blinding arrangements.

6.5. Study Intervention Compliance

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

6.6. 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 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 follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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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.

See Section 8.4.10 for vaccination error reporting requirements, which include administration of an incorrect dosage.

6.9. Prior and Concomitant Therapy

See Section 10.11.6.9 for Substudy A prior and concomitant therapy.

See Section 10.12.6.9 for Substudy B prior and concomitant therapy.

See Section 10.13.6.9 for Substudy C prior and concomitant therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.1.1. Pregnancy

In the case of a positive confirmed pregnancy, the participant will not be administered the study intervention and will be withdrawn from the study.

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;
- Reactogenicity;
- Participant request;
- Investigator request;
- Protocol deviation

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Participants may remain in the study for safety evaluation and be contacted by telephone 6 months after their last study vaccination to record SAEs.

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 their 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;

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- 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 and Baseline 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 participant age will be collected to critically evaluate the immune response and safety profile by age at vaccination.

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.

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8.2. Efficacy and/or Immunogenicity Assessments

8.2.1. Immunogenicity Assessments

See Section 10.11.8.2.1 for Substudy A immunogenicity assessments.

See Section 10.12.8.2.1 for Substudy B immunogenicity assessments.

CCI [redacted]

8.2.2. Biological Samples

Blood and serum 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. 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 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.

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

8.3.1. Physical Examinations

A physical examination will be performed at screening in Substudy C, and may be performed at Visit 101 (Substudy A), Visit 201 (Substudy B), and Visit 301 (Substudy C) prior to vaccination, if clinically indicated. Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

The participant's oral temperature will be measured prior to vaccination in Substudies A and B.

In Substudy C, the participant's body temperature will be measured at screening and prior to vaccination at Visit 301. Additionally, weight, height (at screening), pulse rate, and seated BP will be measured prior to the participants first vaccination in Substudy C.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3. Clinical Safety Laboratory Assessments

Scheduled clinical safety laboratory assessments will be collected in Substudy C.

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

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.4. Reactogenicity Electronic Diary

Participants 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. Participants will be asked to monitor prespecified local reactions and systemic events daily for 7 days, or longer for ongoing events after study vaccination, where Day 1 is the day of vaccination until symptom resolution.

The reactogenicity e-diary allows recording of these assessments each day, thus providing the accurate representation of the participant's experience. 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.

If a participant withdraws because of prespecified event(s) recorded in the e-diary, the event(s) should be recorded on the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

The investigator or designee must obtain stop dates for any symptoms ongoing on the last day the e-diary is completed until resolution. The stop dates should be documented in the source documents and the information entered in the CRF.

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.[40]

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Only an investigator or qualified designee is able to classify a participant's local reaction or systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the participant. If a participant experiences a Grade 4 local reaction or systemic event, the investigator must immediately notify the sponsor. A Grade 4 reaction/event will be collected on the CRF.

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 7-day e-diary collection 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 measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 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. A Grade 4 reaction will be collected on the CRF.

Table 2. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

a. Only an investigator or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. A Grade 4 reaction that meets the definition of an SAE will be collected on the AE CRF.

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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. A Grade 4 event will be collected on CRF.

Table 3. Systemic Event Grading Scale

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

a. Only an investigator or qualified designee is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. A Grade 4 event that meets the definition of an SAE will be collected on the AE CRF.

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8.3.4.4. Fever

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 period, or longer following vaccination, 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)

8.3.5. Pregnancy Testing

Pregnancy testing will be conducted in Substudy A.

Following screening, pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each dose of study intervention. A negative pregnancy test result will be required prior to 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 be withdrawn from administration of study intervention but may remain in the study.

8.3.6. Stopping Rules

Please see Sections 10.11.8.3.1, 10.12.8.3.1, and 10.13.8.3.1, for stopping rules for Substudy A, Substudy B, and Substudy C, respectively.

8.3.7. Electrocardiograms

ECGs will be collected in Substudy C at the times specified in Section 10.13.1.

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Standard 12-lead ECGs will be collected at times specified in the SoA using an ECG system that automatically calculates the HR and measures the PR interval, QT interval, QTcF, and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. The ECGs should be obtained prior to blood collection and collecting BP and pulse rate. ECGs will be performed in triplicate.

ECG data will be submitted to a central laboratory for measurement and interpretation. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8.

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

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 9. 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.

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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 102 in Substudy A, Visit 202 in Substudy B, and Visit 303 in Substudy C.

Additionally, MAEs, NDCMCs, and SAEs will be collected from the time the participant provides informed consent to Visit 103 in Substudy A, Visit 203 in Substudy B, and Visit 304 in Substudy C (approximately 6 months after vaccination). In addition, AEs occurring up to 48 hours after blood draws must be recorded on the CRF.

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 from the study because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported via PSSA.

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 concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer via PSSA.

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 via PSSA immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of 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.

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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 Appendix 3.

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

8.4.3. 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 Appendix 3.

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.

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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 via PSSA, 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 administration of the study intervention.

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- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety via PSSA. 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 report 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 report. 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.

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- 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 via PSSA. 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 report 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 via PSSA, 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 report is maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

The following events are considered AESIs:

- Confirmed diagnosis of influenza (clinical signs/symptoms and positive laboratory testing) after Day 1 through 6 months after vaccination.

- Confirmed diagnosis of myocarditis or pericarditis occurring within 28 days after vaccination. See Section 10.11.8.10.5, Section 10.12.8.10.5, and Section 10.13.8.10.7 for additional procedures for monitoring of potential myocarditis or pericarditis.

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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 via PSSA.

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 Appendix 9.

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 Appendix 3 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.

Refer to Section 10.9.4 for instructions for documenting and reporting medical device deficiencies.

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8.4.9.2. 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.

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.

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.

Vaccination errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported via PSSA 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;

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- 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.

Whether or not the vaccination error is accompanied by an AE, as determined by the investigator, such vaccination errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) 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 via PSSA **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

CCI [redacted]

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

See Section 8.2.1.

8.9. Health Economics

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

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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 described 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.

Statistical considerations that apply to all substudies in this protocol are detailed below; please see the statistical considerations appendix for details that apply to each specific substudy:

See Section 10.11.9 for Substudy A statistical considerations.

See Section 10.12.9 for Substudy B statistical considerations.

See Section 10.13.9 for Substudy C statistical considerations.

9.1. Statistical Hypotheses

Refer to Section 10.11.9.1, Section 10.12.9.1, and Section 10.13.9.1 for Substudy A, Substudy B, and Substudy C statistical hypotheses, respectively.

9.1.1. Estimands

Refer to Section 10.11.9.1.1, Section 10.12.9.1.1, and Section 10.13.9.1.1 for estimands relating to Substudy A, Substudy B, and Substudy C, respectively.

9.1.2. Multiplicity Adjustment

Refer to Section 10.11.9.1.2, Section 10.12.9.1.2, and Section 10.13.9.1.2 for multiplicity adjustment for Substudy A, Substudy B, and Substudy C, respectively.

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.
CCI	[redacted]

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Population	Description
CCI [redacted]	[redacted]
Safety	All participants who receive the study intervention.

9.3. Statistical Analyses

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

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 [redacted], the analysis will be based on the evaluable immunogenicity population. Antibody titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for 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 population (HAIs CCI [redacted] 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.

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9.3.1.1. Analysis for Binary Data

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

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

9.3.1.2. Analysis 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 the Student 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 of 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 the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.2.3. 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. Safety Analyses

All safety analyses will be performed on the safety population.

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9.4. Interim Analyses

There are no formal interim analyses planned for any of the substudies. As each substudy is open-label to the sponsor, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, dose selection, and/or supporting clinical development.

9.5. Sample Size Determination

Refer to Section 10.11.9.5, Section 10.12.9.5, and Section 10.13.9.5 for sample size determination for Substudy A, Substudy B, and Substudy C, respectively.

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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.

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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.

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

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

10.1.3.1. Electronic Consent

Participants may be able to experience the informed consent process by electronic means (eConsent). The eConsent process includes an electronic presentation of the informed consent document (eICD), clinical trial educational components (as applicable), and electronic signatures (if allowed by local regulations). The use of eConsent does not replace or alter the ICD content or informed consent process as described above. The eConsent process complies with applicable regulations and sponsor policies to ensure reliability and data privacy.

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 not use an EDMC.

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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 18 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.

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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 records and 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.

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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 a source document 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 record) 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. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be reidentified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

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- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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.

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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.

10.1.11. 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.

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10.1.12. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the investigator site file or equivalent.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) PI contact information.

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10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in Section 10.13.1 for Substudy C. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood.

Substudy C	
Hematology	**Chemistry**
N/A	Cardiac troponin I

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

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

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

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal 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.

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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.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening 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.

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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.

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs via PSSA 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 PSSA 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 PSSA for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported via PSSA 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 SAE) is reported to Pfizer Safety via PSSA.
** **EDB** is reported to Pfizer Safety via PSSA, 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 via PSSA.

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- 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 Report 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. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- 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:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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.

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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.

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- 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 PSSA 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.

10.3.4. 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 (eg, eSAE or PSSA).
- If the electronic system is unavailable, then the site will use the paper SAE report form (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.

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- 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 Report Form

- Facsimile transmission of the Vaccine SAE Report Form is the backup method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours.
- 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 Report 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 Report Form pages within the designated reporting time frames.

10.3.5. Newly Diagnosed Chronic Medical Conditions

An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects (eg, asthma).

10.3.6. Medically Attended AE

An MAE is defined as a nonserious AE that results in an evaluation at a medical facility.

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10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse 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.

10.4.2. 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 10.4.4 for a complete list of contraceptive methods permitted in the study.

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

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

  OR

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

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

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10.4.3. Woman of Childbearing Potential

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

If fertility is unclear (eg, amenorrhea or oligomenorrhea) 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.

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10.4.4. Contraception Methods

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

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

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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).

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10.5. Appendix 5: Genetics

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

Potential Cases of Drug-Induced Liver Injury

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

LFTs are not required as a routine safety monitoring procedure in 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).

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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, eosinophils (%), 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, total bile acids, 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.

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10.7. Appendix 7: Kidney Safety Monitoring Guidelines

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

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Screat increase. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated.

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat-only based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat-only based equation (see the table in Section 10.7.2.1) and by combined Screat plus Scys-based equation. When postbaseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable postbaseline comparison of eGFR changes (Screat-only based eGFR and combined Screat plus Scys eGFR).

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.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

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

eGFR (mL/min/1.73m²)

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

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10.7.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at the screening, baseline, and postbaseline visits. Site calculations of kidney function can be performed manually, using the age-appropriate formulae (see Section 10.7.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units are used for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer clinical team and medical monitor, if needed.

10.7.4. 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 for both pediatric and adult participants.

KDIGO Criteria Grade (G)	Study Population	G1	G2	G3	G4	G5
Decreased Kidney Function Due to Either Acute or Chronic Kidney Injury	Adult participants eGFR (mL/min/1.73m²)	≥90	≥60 to 89	30 to 59	15 to 29	<15
	Pediatric participants eCrCl (mL/min)	≥90	≥60 to 89	30 to 59	15 to 29	<15 OR dialysis indicated

KDIGO Albuminuria (A) Criteria	A1	A2	A3
Albumin-to-Creatinine Ratio (ACR)	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

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10.8. Appendix 8: 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). • New prolongation of QTcF 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-second 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.
• Absolute value of QTcF >450 ms AND QTcF change from baseline >60 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 asystolic pauses ≥3 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 asystolic pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

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- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30-second 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-second 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 major events of potential clinical concern listed above 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 is to be reported as AEs/SAEs.

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10.9. Appendix 9: 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).

10.9.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Section 10.3.1. • 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.

10.9.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Section 10.3.2.
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.

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

10.9.3. 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.

10.9.4. 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. • 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. • The unblinded site staff will notify the sponsor study team by telephone, email, or other contact method within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency. • The sponsor study team will capture the required information on the Medical Device Complaint form along with any associated AE (either serious or nonserious) when applicable and send to the appropriate product quality complaint group.

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- 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. All relevant details related to the role of the device in regard to the SAE must be included in the Vaccine SAE Report Form as outlined in Section 8.4.1.1 and Section 8.4.1.2.

- 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. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

- For device deficiencies, it is very important that the investigator 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.

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- 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

- Follow-up applies to all participants, including those who discontinue study intervention.
- 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 by the sponsor study team.
- 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 Report Form within 24 hours of receipt of the information, according to the requirements provided in Section 10.3.

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10.10. Appendix 10: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

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

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

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

Known HBV infection

- Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:
- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation

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10.11. Appendix 11: Substudy A

10.11.1. SoA – Substudy A

Visit Number	101	102	103
Visit Description	**Vaccination**	**4-Week Follow-Up Visit**	**6-Month Follow-Up Visit**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 101**	**175 to 189 Days After Visit 101**
Visit Type/Location	**Site**	**Site**	**Site**
Obtain informed consent	X		
Perform VCT verification process, if applicable	X		
Assign participant number	X		
Obtain demography and medical history	X		
Perform clinical assessment[a]	X		
Collect nonstudy vaccine information	X	X	X
Collect information regarding last dose of licensed influenza vaccine, and prior receipt of any mRNA vaccine	X		
Collect prohibited medication use		X	X
Confirm use of contraceptives (if appropriate)	X	X	
Measure oral temperature	X		
Perform urine pregnancy test on WOCBP	X		
Confirm eligibility	X		
Review temporary delay criteria	X		
Collect blood sample CCI [redacted]	~30 mL	~30 mL	~30 mL
Obtain randomization number and study intervention allocation	X		
Administer study intervention	X		
Postvaccination observation (at least 30 minutes) and assessment of immediate events	X		
Explain reactogenicity e-diary completion, 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		
Site review of e-diary data with participant follow-up until ongoing event resolution, if applicable[b]	←	→	
Collect AEs, MAEs, NDCMCs, and SAEs as appropriate[c]	X	X	X
Collect e-diary or assist the participant with deleting application		X	

a. Including, if indicated, a physical examination.
b. Between visits, review the e-diary data online at frequent intervals. Contact the participant in order to obtain stop dates for any prespecified local reactions or systemic events. Assess any medically attended reactogenicity events (including hospitalizations) and e-diary compliance.
c. AEs are collected from the completion of informed consent to Visit 102. MAEs, NDCMCs, and SAEs are collected from the completion of informed consent to Visit 103 (approximately 6 months after vaccination). Additionally, any AEs occurring up to 48 hours after a blood draw must be recorded.

10.11.2. Introduction (Substudy A)

10.11.2.1. Substudy A Rationale

Ongoing and completed influenza modRNA vaccine studies demonstrated attenuated influenza B strain responses in adults 18 through 64 years of age. Substudy A is a Phase 2, randomized, active-controlled, observer-blinded (sponsor-unblinded) study to assess the safety, tolerability, and immunogenicity of different formulations and doses of tIRV (2×A, 1×B) aimed at enhancing the immunogenicity against influenza B strains compared to a licensed CCI influenza vaccine. This substudy will be conducted in adults 18 through 64 years of age and will assess the following formulations and doses of tIRV:

- tIRV1 (preformulated) – CCI
- tIRV2 (separate LNPs for each strain) – CCI
- tIRV3 (separate LNPs for each strain) – CCI

This substudy will inform the choice of the optimized influenza modRNA vaccine reformulation that may be further studied in adults 18 through 64 years of age.

See Section 10.11.4 for more details regarding the design.

10.11.2.2. Background

See Section 2.2.

10.11.2.3. Benefit/Risk Assessment

Besides those risks detailed in Section 2.7, no additional risks are noted for Substudy A.

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10.11.3. Objectives, Endpoints, and Estimands (Substudy A)

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To define the safety and tolerability profile of tIRVs in participants 18 through 64 years of age	• 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 • MAEs • NDCMCs	In participants receiving study intervention (safety population), the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs through 4 weeks after vaccination • MAEs through 6 months after vaccination • NDCMCs through 6 months after vaccination • SAEs through 6 months after vaccination
Secondary:	**Secondary:**	**Secondary:**
To describe the immune response elicited by tIRVs in participants 18 through 64 years of age	• HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI [redacted] influenza vaccines	In participants complying with the key protocol criteria (evaluable immunogenicity population [HAI CCI [redacted]]): • HAI GMTs at baseline and 4 weeks after vaccination • HAI GMFRs from before vaccination to 4 weeks after vaccination • The proportion of participants achieving HAI seroconversion[a] 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
CCI [redacted]		

Objectives	Endpoints	Estimands
CCI		

a. 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 at least a 4-fold rise at the time point of interest.

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10.11.4. Substudy A Design

10.11.4.1. Overall Design

This is a Phase 2, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, and immunogenicity of 3 different formulations of tIRV (tIRV1 through tIRV3) encoding HA for the targeted seasonal influenza strains compared to QIV1 (CCI [redacted]) and qIRV1 (encoding HA for 2 A and 2 B seasonal influenza strains) in healthy adults 18 through 64 years of age.

Up to approximately 450 participants 18 through 64 years of age will be enrolled and randomized to receive 1 dose of study intervention as shown in Table 5. Depending on the availability of study intervention and operational prioritization, study intervention groups may not all be randomized concurrently; however, a minimum of 2 groups will be open for randomization at any one time.

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Table 5. Number of Participants to Be Enrolled in Substudy A – Participants 18 Through 64 Years of Age

Study Intervention Group	Age Stratum (Years)	Study Intervention	Preformulated[a]	Influenza Strains	CCI	Total modRNA Dose	Number of Participants
1A	18 through 64	QIV1	Yes	2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI [redacted] influenza vaccines	[redacted]	N/A	90
2A	18 through 64	tIRV1	Yes	A/H1N1	[redacted]	CCI [redacted]	90
				A/H3N2			
				B/Victoria			
3A	18 through 64	tIRV2	No	A/H1N1			90
				A/H3N2			
				B/Victoria			
4A	18 through 64	tIRV3	No	A/H1N1			90
				A/H3N2			
				B/Victoria			
5A	18 through 64	qIRV1	Yes	A/H1N1			90
				A/H3N2			
				B/Victoria			
				B/Yamagata			

a. For tIRV2 and tIRV3 (which are not preformulated), mIRVs encoding HA for each A and B strain will be mixed at the site to generate these study interventions at the dose-level combination shown. Please see the IPM for further details.

Blood samples of approximately 30 mL will be collected [redacted] prior to vaccination and at 4 weeks and 6 months after vaccination.

Local reaction and systemic event data will be collected in an e-diary during the 7-day follow-up period, or longer for ongoing symptoms, after study vaccination (ie, from Day 1, the day of vaccination, until event resolution).

All AEs will be collected from informed consent signing through 4 weeks following vaccination. A subset of AEs (NDCMCs, MAEs, 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 will be collected.

Stopping rules will apply as detailed in Section 10.11.8.3.1.

10.11.4.2. Scientific Rationale for Study Design

See Section 2.1.

10.11.4.3. Justification for Dose

See Section 4.3.

10.11.4.4. End of Substudy Definition

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

A participant is considered to have completed the substudy if they have completed the last visit (Visit 103).

10.11.5. Substudy A Population

10.11.5.1. Substudy A Inclusion Criteria

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

Age and Sex:

1. Participants 18 (or the minimum age of consent in accordance with local regulations if older than 18 years) through 64 years of age at Visit 101 (Day 1).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Disease Characteristics:

Not applicable.

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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 10.10.

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.

10.11.5.2. Substudy A Exclusion Criteria

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

Medical Conditions:

1. Diagnosed with influenza by an FDA-approved testing method ≤180 days before study intervention administration.

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. Women who are pregnant or breastfeeding.

6. Prior history of myocarditis or pericarditis.

7. Any 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.

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Prior/Concomitant Therapy:

8. Receipt of chronic medications with known systemic immunosuppressant effects (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before enrollment.

   Note: Systemic corticosteroids when 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 meet this criterion. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

10. Any participant who has received investigational or licensed influenza vaccination within 6 months (180 days) before study intervention administration.

11. Receipt of chronic antiviral therapy with activity against influenza.

Prior/Concurrent Clinical Study Experience:

12. Participation in other studies involving administration of an investigational product within 28 days prior to, and/or during, participation in this study. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

13. 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.

10.11.5.3. Lifestyle Considerations

See Section 5.3.

10.11.5.4. Screen Failures

See Section 5.4.

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

The following conditions may allow a participant to be enrolled once the conditions have resolved and the participant is otherwise eligible:

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 28 days before study intervention administration at Visit 101.

3. Anticipated receipt of any nonstudy vaccine within 28 days after study intervention administration at Visit 101.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration at Visit 101 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.

10.11.6. Substudy A Intervention and Concomitant Therapy

10.11.6.1. Study Intervention(s) Administered

Intervention Name	**tIRV**	**qIRV1**	**QIV1** (CCI)
Type	Vaccine	Vaccine	Vaccine
Use	Experimental	Experimental	Comparator
IMP or NIMP/AxMP	IMP	IMP	IMP
Dose Formulation	Solution for injection	Solution for injection	Solution for injection
modRNA Unit Dose Strength(s)	tIRV1: CCI tIRV2 CCI tIRV3:	qIRV1: CCI	N/A
Targeted Influenza Strains	As recommended by WHO for CCI vaccines (2023-2024 northern hemisphere influenza season),[1] ie, CCI	As recommended by WHO for CCI vaccines (2023–2024 northern hemisphere influenza season)[1], ie,	As recommended by WHO for CCI vaccines (2023-2024 northern hemisphere influenza season)
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Sourcing	tIRV1: Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor

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Intervention Name	tIRV	qIRV1	QIV1 (CCI)
	tIRV2 and tIRV3: mIRVs encoding HA for each A and B strain will be mixed at the site to generate tIRV at the relevant dose-level combination. Please see the IPM for further details.		
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 either as a PFS or in a glass vial as open-label supply. Each PFS/vial will be labeled as required per country requirement.	Study intervention will be provided either as a PFS or in a glass vial as open-label supply. Each PFS/vial will be labeled as required per country requirement.
SRSD	IB	IB	CCI USPI

10.11.6.1.1. Administration

Participants will receive 1 dose of study intervention at Visit 101 in accordance with the study's SoA (Section 10.11.1). Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm. Study intervention will be administered by an **unblinded** administrator.

10.11.6.2. Preparation, Handling, Storage, and Accountability

See Section 6.2.

10.11.6.3. Assignment to Study Intervention

See Section 6.3.

10.11.6.4. Blinding

10.11.6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

10.11.6.4.2. 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 the study interventions, these will be administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

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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.

10.11.6.4.3. Blinding of the Sponsor

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

10.11.6.4.4. 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 vaccine 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 vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

10.11.6.5. Study Intervention Compliance

See Section 6.5.

10.11.6.6. Dose Modification

Not applicable.

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

See Section 6.7.

10.11.6.8. Treatment of Overdose

See Section 6.8.

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10.11.6.9. Prior and Concomitant Therapy

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Section 10.4).

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

- Any vaccinations received from 28 days prior to study enrollment until the last visit (Visit 103).
- Last dose of licensed influenza vaccine, if received.
- Prior receipt of any mRNA vaccine (eg, mRNA-based COVID-19 vaccine).
- Prohibited medications listed in Section 10.11.6.9.1, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

10.11.6.9.1. 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 7.2). Medications should not be withheld if required for a participant's medical care.

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after study vaccination at Visit 101.
- Receipt of any mRNA vaccine within 28 days before and 28 days after study vaccination at Visit 101.
- Receipt of any other (nonstudy) seasonal influenza vaccine after study intervention administration through completion of the study.
- Receipt of chronic medications with known systemic immunosuppressant effects, or radiotherapy, within 60 days before enrollment through conclusion of the study.
- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 60 days prior to enrollment through 28 days after administration of the study intervention.

  Note: Receipt of short term (<14 days) systemic corticosteroids at a dose of ≥20 mg/day of prednisone or equivalent is prohibited from enrollment through 28 days after administration of study intervention.
- Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

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- 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.

10.11.6.9.2. Permitted During the Study

- Medication other than that described as prohibited in Section 10.11.6.9.1 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.

10.11.7. Discontinuation of Substudy A Intervention and Participant Discontinuation/Withdrawal

See Section 7.

10.11.8. Substudy A Assessments and Procedures

10.11.8.1. Administrative and Baseline Procedures

See Section 8.1.

The minimal blood sampling volume for individual participants in this study is approximately 90 mL (30 mL at Visits 101, 102, and 103).

10.11.8.2. Efficacy and/or Immunogenicity Assessments

10.11.8.2.1. Immunogenicity Assessments

Samples will be collected at time points specified in Section 10.11.1 and the following assays will be run:

- HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI [redacted] influenza vaccines.

On a randomly generated subset of samples, the sponsor may conduct the following assessments assays:

CCI [redacted]

10.11.8.3. Safety Assessments

See Section 8.3.

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10.11.8.3.1. Stopping Rules for Substudy A

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

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

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

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

A stopping rule is met if either of the following rules occurs **within 4 weeks** after administration of study intervention.

Targeted Cardiac Abnormalities

1. If any participant vaccinated with tIRV or qIRV develops a suspected or confirmed diagnosis of myocarditis or pericarditis.

Death

2. If any participant vaccinated with tIRV or qIRV dies following administration of study intervention, irrespective of investigator assessment of relatedness.

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

See Section 8.4.

10.11.8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

10.11.8.6. Genetics

See Section 8.6.

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10.11.8.7. Biomarkers

Biomarkers are not evaluated in this study.

10.11.8.8. Immunogenicity Assessments

See Section 10.11.8.2.1.

10.11.8.9. Health Economics

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

10.11.8.10. Substudy A Procedures

10.11.8.10.1. Visit 101 – 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 their 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 on the day of study intervention administration.

- Perform the VCT verification process, if applicable. This process helps ensure Pfizer clinical data quality and participant safety in trials by aiding investigational sites in the monitoring for and halting of dual enrollment of participants.
- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including age in years, sex, race, and ethnicity).
- 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.
- Record nonstudy vaccinations as described in Section 10.11.6.9.
- Record prior receipt of any mRNA vaccine (eg, mRNA-based COVID-19 vaccine), as described in Section 10.11.6.9.
- Record information on the last dose of licensed influenza vaccine, as described in Section 10.11.6.9.

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- If applicable, discuss contraceptive use as described in Section 10.4.

On the day of and prior to study intervention administration:

- Measure the participant's oral temperature.
- On the day of and prior to study intervention administration, perform a pregnancy test on WOCBP as described in Section 8.3.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 10.11.5.5.
- Collect a blood sample (approximately 30 mL), before administration of study intervention, CCI [redacted]
- Obtain the participant's randomization number and study intervention allocation using the IRT system.
- 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.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute events. Record any acute reactions (including time of onset) in the participant's source documents, on the CRF, and via PSSA as applicable.
- Assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
- Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, or longer, until any ongoing symptoms are resolved, with Day 1 being the day of vaccination.
- Provide a measuring device to measure local reactions at the injection site, and a thermometer for recording daily temperatures during the e-diary period; provide instructions on their use.
- 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).

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  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Record AEs as described in Section 8.4.
- 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.
- Remind participants that study staff may contact them to obtain additional information on symptoms entered into the e-diary until the symptoms resolve.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.11.8.10.5).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.11.8.10.2. Visit 102 – 4-Week Follow-Up Visit (After Vaccination) – 28 to 35 Days After Visit 101

- Record AEs, MAEs, SAEs, and NDCMCs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 10.11.6.9.
- Record prohibited medication use as described in Section 10.11.6.9.1.
- If applicable, discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 30 mL [redacted]

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- Review the participant's e-diary data and record assessment in the CRF. Assess compliance, record any medically attended events (including hospitalizations), and collect stop dates for any local reaction or systemic event ongoing since the 7-day follow-up period after vaccination. Document in the CRF.
    - For any ongoing local reactions or systemic events, the site will follow up until resolution and document and record stop dates in the CRF.
- Collect the participant's e-diary or assist the participant with removing the study application from their own personal device.
- 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.
- 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.

10.11.8.10.3. Visit 103 – 6-Month Follow-Up Visit (After Vaccination) – 175 to 189 Days After Visit 101

- Record MAEs, SAEs, and NDCMCs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 10.11.6.9.
- Record prohibited medication use as described in Section 10.11.6.9.1.
- Collect a blood sample of approximately 30 mL [redacted]
- 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.

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10.11.8.10.4. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.3.4.2), Grade 3 systemic event (Section 8.3.4.3), or fever ≥39.0°C (≥102.1°F) (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 >40.0°C (>104.0°F) (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.
- The investigator or appropriate designee confirmed severe reactogenicity assessment via medical records and/ or telehealth assessment.

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.

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- 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.

10.11.8.10.5. 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 28 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 via central laboratory (Note: In addition to central ECG interpretation, local ECG and troponin interpretation may be used to inform decision making necessary to ensure the immediate safety of participants.):

- ECG and

- Measurement of the troponin I 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.

10.11.9. Substudy A Statistical Considerations

10.11.9.1. Statistical Hypotheses

There are no statistical hypotheses in Substudy A.

10.11.9.1.1. Estimands

The estimands corresponding to the primary, secondary, CCI [redacted] objectives are described in the table in Section 10.11.3.

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10.11.9.1.2. Multiplicity Adjustment

There is no multiplicity adjustment for Substudy A, as all analyses are descriptive in nature.

10.11.9.2. Analysis Sets

See Section 9.2 for defined analysis sets.

10.11.9.3. Statistical Analyses

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

10.11.9.3.1. General Considerations

See Section 9.3.1 for general considerations of statistical analyses.

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

Endpoint	Statistical Analysis Methods
Safety	• Point estimates and the associated exact 2-sided 95% CIs for the proportion of participants reporting each event (local reactions, systemic events) for up to 7 days after vaccination calculated by the Clopper-Pearson method will be provided for each vaccine group. • Point estimates and the associated exact 2-sided 95% CIs for the proportion of participants reporting each AE through 4 weeks after vaccination calculated by the Clopper-Pearson method will be provided for each vaccine group. • Point estimates and the associated exact 2-sided 95% CIs for the proportion of participants reporting each event (AEs, SAEs, MAEs, NDCMCs) through 6 months after vaccination calculated by the Clopper-Pearson method will be provided for each vaccine group.

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

Endpoint	Statistical Analysis Methods
Immunogenicity (HAIs CCI [redacted])	• HAI GMTs and associated 2-sided 95% CIs will be provided for each strain, by vaccine group, at baseline and 4 weeks after vaccination. • HAI GMFRs from before vaccination to 4 weeks after vaccination, and associated 2-sided 95% CIs, will be provided for each strain, by vaccine group.

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Endpoint	Statistical Analysis Methods
	• The proportion of participants achieving HAI seroconversion at 4 weeks after vaccination, and associated 2-sided Clopper-Pearson 95% CIs, will be provided for each strain, by vaccine group. • The proportion of participants with HAI titers ≥1:40 and associated 2-sided Clopper-Pearson 95% CIs will be provided for each strain, by vaccine group, at baseline and 4 weeks after vaccination.

10.11.9.3.4. CCI [redacted] Endpoint(s)

Endpoint	Statistical Analysis Methods
CCI [redacted]	The statistical methods used for the related endpoints will be defined in the study SAP.

10.11.9.3.5. Other Analyses

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis within 28 days after a study vaccination (ECG, troponin I level, cardiac echocardiogram, and/or cardiac magnetic resonance study) will be summarized and listed by vaccine group.

10.11.9.4. Interim Analyses

As the study is open-label to the sponsor, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, dose selection, and/or supporting clinical development.

10.11.9.5. Sample Size Determination

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

Approximately 90 participants will be enrolled in each vaccine group; therefore, a total of approximately up to 450 participants may be enrolled into this substudy.

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For safety outcomes in the study, Table 6 shows the probability of observing at least 1 AE for a given true event rate of a particular AE with 90 participants in each vaccine group.

Table 6. Probability of Observing at Least 1 AE by Assumed True Event Rate

Sample Size	Assumed True Rate of an AE	Probability of Observing at Least 1 AE
90	0.5%	36.3%
	1.0%	59.5%
	2.0%	83.8%
	5.0%	99.0%
	7.0%	99.9%

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10.12. Appendix 12: Substudy B

10.12.1. SoA – Substudy B

Visit Number	201	202	203
Visit Description	**Vaccination**	**4-Week Follow-Up Visit**	**6-Month Follow-Up Visit**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 201**	**175 to 189 Days After Visit 201**
Visit Type/Location	**Site**	**Site**	**Site**
Obtain informed consent	X		
Perform VCT verification process, if applicable	X		
Assign participant number	X		
Obtain demography and medical history	X		
Perform clinical assessment[a]	X		
Collect nonstudy vaccine information	X	X	X
Collect information regarding last dose of prior licensed influenza vaccine and prior receipt of any mRNA vaccine	X		
Collect prohibited medication use		X	X
Confirm use of contraceptives (if appropriate)	X	X	
Measure oral temperature	X		
Confirm eligibility	X		
Review temporary delay criteria	X		
Collect blood sample [redacted]	~30 mL	~30 mL	~30 mL
Obtain randomization number and study intervention allocation	X		
Administer study intervention	X		
Postvaccination observation (at least 30 minutes) and assessment of immediate events	X		
Explain reactogenicity e-diary completion, 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		
Site review of e-diary data with participant follow-up until ongoing event resolution, if applicable[b]	◄	——— ►	
Collect AEs, MAEs, NDCMCs, and SAEs as appropriate[c]	X	X	X
Collect e-diary or assist the participant with deleting application		X	

a. Including, if indicated, a physical examination.
b. Between visits, review the e-diary data online at frequent intervals. Contact the participant in order to obtain stop dates for any prespecified local reactions or systemic events. Assess any medically attended reactogenicity events (including hospitalizations) and e-diary compliance.
c. AEs are collected from the completion of informed consent to Visit 202. MAEs, NDCMCs, and SAEs are collected from the completion of informed consent to Visit 203 (approximately 6 months after vaccination). Additionally, any AEs occurring up to 48 hours after a blood draw must be recorded.

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10.12.2. Introduction (Substudy B)

10.12.2.1. Substudy B Rationale

Ongoing and completed influenza modRNA vaccine studies have demonstrated attenuated influenza B strain responses in older adults (≥65 years of age). Substudy B is a Phase 2, randomized, active-controlled, observer-blinded (sponsor-unblinded) study to assess the safety and immunogenicity of different formulations and doses of tIRV (2×A, 1×B) to enhance the immunogenicity against influenza B strains compared to a licensed CCI influenza vaccine. The substudy will be conducted in older adults (≥65 years of age) and will assess the following formulations and doses of tIRV:

- tIRV2 (separate LNPs for each strain) – CCI
- tIRV3 (separate LNPs for each strain) – CCI

This substudy will inform the choice of the optimized influenza modRNA vaccine reformulation that may be further studied older adults (≥65 years of age).

See Section 10.12.4 for more details regarding the design.

10.12.2.2. Background

See Section 2.2.

10.12.2.3. Benefit/Risk Assessment

Besides those risks detailed in Section 2.7, no additional risks are noted for Substudy B.

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10.12.3. Objectives, Endpoints, and Estimands (Substudy B)

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To define the safety and tolerability profile of tIRVs in participants ≥65 years of age	• 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 • MAEs • NDCMCs	In participants receiving study intervention (safety population), the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs through 4 weeks after vaccination • MAEs through 6 months after vaccination • NDCMCs through 6 months after vaccination • SAEs through 6 months after vaccination
Secondary:	**Secondary:**	**Secondary:**
To describe the immune response elicited by tIRVs in participants ≥65 years of age	• HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI [redacted] influenza vaccines	In participants complying with the key protocol criteria (evaluable immunogenicity population [HAI CCI [redacted]]): • HAI GMTs at baseline and 4 weeks after vaccination • HAI GMFRs from before vaccination to 4 weeks after vaccination • The proportion of participants achieving HAI seroconversion[a] 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

Objectives	Endpoints	Estimands
CCI		

a. 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 at least a 4-fold rise at the time point of interest.

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10.12.4. Substudy B Design

10.12.4.1. Overall Design

This is a Phase 2, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, and immunogenicity of 2 different formulations of tIRV (tIRV2 and tIRV3) encoding HA for the targeted seasonal influenza strains compared to QIVs CCI and qIRV (encoding HA for 2 A and 2 B seasonal influenza strains) in healthy adults ≥65 years of age.

Up to approximately 450 participants ≥65 years of age will be enrolled and randomized to receive 1 dose of study intervention as shown in Table 7. Depending on the availability of study intervention and operational prioritization, study intervention groups may not all be randomized concurrently; however, a minimum of 2 groups will be open for randomization at any one time.

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Table 7. Number of Participants to Be Enrolled in Substudy B – Participants ≥65 Years of Age

Study Intervention Group	Age Stratum	Study Intervention	Preformulated[a]	Influenza Strains	CCI	Total modRNA Dose	Number of Participants
1B	≥65	QIV2	Yes	2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI influenza vaccines		N/A	90
2B	≥65	QIV3	Yes	2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI influenza vaccines		N/A	90
3B	≥65	tIRV2	No	A/H1N1		CCI	90
				A/H3N2			
				B/Victoria			
4B	≥65	tIRV3	No	A/H1N1			90
				A/H3N2			
				B/Victoria			
5B	≥65	qIRV2	Yes	A/H1N1			90
				A/H3N2			
				B/Victoria			
				B/Yamagata			

a. For tIRV2 and tIRV3 (which are not preformulated), mIRVs encoding HA for each A and B strain will be mixed at the site to generate these study interventions at the dose-level combination shown. Please see the IPM for further details

Blood samples of approximately 30 mL will be collected [redacted] prior to vaccination and at 4 weeks and 6 months after vaccination.

Local reaction and systemic event data will be collected in an e-diary during the 7-day follow-up period, or longer for ongoing symptoms, after study vaccination (ie, from Day 1, the day of vaccination, until event resolution).

AEs will be collected from informed consent signing through 4 weeks following vaccination; NDCMCs, MAEs, 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 will be collected.

Stopping rules will apply as detailed in Section 10.12.8.3.1.

10.12.4.2. Scientific Rationale for Study Design

See Section 2.1.

10.12.4.3. Justification for Dose

See Section 4.3.

10.12.4.4. End of Substudy Definition

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

A participant is considered to have completed the substudy if they have completed the last visit (Visit 203).

10.12.5. Substudy B Population

10.12.5.1. Substudy B Inclusion Criteria

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

Age and Sex:

1. Participants ≥65 years of age at Visit 201 (Day 1).

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Disease Characteristics:

Not applicable.

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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 10.10.

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.

10.12.5.2. Substudy B Exclusion Criteria

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

Medical Conditions:

1. Diagnosed with influenza by an FDA-approved testing method ≤180 days before study intervention administration.

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. Prior history of myocarditis or pericarditis.

6. Any 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.

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Prior/Concomitant Therapy:

7. Receipt of chronic medications with known systemic immunosuppressant effects (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before enrollment.

   Note: Systemic corticosteroids when 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 meet this criterion. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

9. Any participant who has received investigational or licensed influenza vaccination within 6 months (180 days) before study intervention administration.

10. Receipt of chronic antiviral therapy with activity against influenza.

Prior/Concurrent Clinical Study Experience:

11. Participation in other studies involving administration of an investigational product within 28 days prior to, and/or during, participation in this study. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

12. 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.

10.12.5.3. Lifestyle Considerations

See Section 5.3.

10.12.5.4. Screen Failures

See Section 5.4.

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

The following conditions may allow a participant to be enrolled once the conditions have resolved and the participant is otherwise eligible:

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 28 days before study intervention administration at Visit 201.

3. Anticipated receipt of any nonstudy vaccine within 28 days after study intervention administration at Visit 201.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration at Visit 201 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.

10.12.6. Substudy B Intervention and Concomitant Therapy

10.12.6.1. Study Intervention(s) Administered

Intervention Name	**tIRV**	**qIRV2**	**QIV2** CCI	**QIV3** (CCI)
Type	Vaccine	Vaccine	Vaccine	Vaccine
Use	Experimental	Experimental	Comparator	Comparator
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP
Dose Formulation	Solution for injection	Solution for injection	Solution for injection	Solution for injection
modRNA Unit Dose Strength(s)	tIRV2: CCI tIRV3:	qIRV2: CCI	N/A	N/A
Targeted Influenza Strains	As recommended by WHO for CCI vaccines (2023-2024 northern hemisphere influenza season)[1], ie, CCI	As recommended by WHO for CCI vaccines (2023-2024 northern hemisphere influenza season)[1], ie,	As recommended by WHO for CCI vaccines (2023-2024 northern hemisphere influenza season)	As recommended by WHO for CCI vaccines (2023-2024 northern hemisphere influenza season)
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection

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Intervention Name	tIRV	qIRV2	QIV2 (CCI [redacted]	QIV3 CCI [redacted]
Sourcing	mIRVs encoding HA for each A and B strain will be mixed at the site to generate tIRV at the relevant dose-level combination. Please see the IPM for further details.	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
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 either as a PFS or in a glass vial as open-label supply. Each PFS/vial will be labeled as required per country requirement.	Study intervention will be provided either as a PFS or in a glass vial as open-label supply. Each PFS/vial will be labeled as required per country requirement.	Study intervention will be provided either as a PFS or in a glass vial as open-label supply. Each PFS/vial will be labeled as required per country requirement.
SRSD	IB	IB	CCI [redacted] USPI	CCI [redacted] USPI

10.12.6.1.1. Administration

Participants will receive 1 dose of study intervention at Visit 201 in accordance with the study's SoA (Section 10.12.1). Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm. Study intervention will be administered by an **unblinded** administrator.

10.12.6.2. Preparation, Handling, Storage, and Accountability

See Section 6.2.

10.12.6.3. Assignment to Study Intervention

See Section 6.3.

10.12.6.4. Blinding

10.12.6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

10.12.6.4.2. 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 the study interventions, these will be administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

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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.

10.12.6.4.3. Blinding of the Sponsor

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

10.12.6.4.4. 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 vaccine 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 vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

10.12.6.5. Study Intervention Compliance

See Section 6.5.

10.12.6.6. Dose Modification

Not applicable.

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

See Section 6.7.

10.12.6.8. Treatment of Overdose

See Section 6.8.

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10.12.6.9. Prior and Concomitant Therapy

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Section 10.4).

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

- Any vaccinations received from 28 days prior to study enrollment until the last visit (Visit 203).
- Last dose of licensed influenza vaccine, if received.
- Prior receipt of any mRNA vaccine (eg, mRNA-based COVID-19 vaccine).
- Prohibited medications listed in Section 10.12.6.9.1, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

10.12.6.9.1. 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 7.2). Medications should not be withheld if required for a participant's medical care.

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after study vaccination at Visit 201.
- Receipt of any mRNA vaccine within 28 days before and 28 days after study vaccination at Visit 201.
- Receipt of any other (nonstudy) seasonal influenza vaccine after study intervention administration through completion of the study.
- Receipt of chronic medications with known systemic immunosuppressant effects, or radiotherapy, within 60 days before enrollment through conclusion of the study.
- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 60 days prior to enrollment through 28 days after administration of the study intervention.

  Note: Receipt of short term (<14 days) systemic corticosteroids at a dose of ≥20 mg/day of prednisone or equivalent is prohibited from enrollment through 28 days after administration of study intervention.
- Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

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- 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.

10.12.6.9.2. Permitted During the Study

- Medication other than that described as prohibited in Section 10.12.6.9.1 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.

10.12.7. Discontinuation of Substudy B Intervention and Participant Discontinuation/Withdrawal

See Section 7.

10.12.8. Substudy B Assessments and Procedures

10.12.8.1. Administrative and Baseline Procedures

See Section 8.1.

The minimal blood sampling volume for individual participants in this study is approximately 90 mL (30 mL at Visits 201, 202, and 203).

10.12.8.2. Efficacy and/or Immunogenicity Assessments

10.12.8.2.1. Immunogenicity Assessments

Samples will be collected at time points specified in Section 10.12.1 and the following assays will be run:

- HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI [redacted] influenza vaccines.

CCI [redacted]

On a randomly generated subset of samples, the sponsor may conduct the following assessments assays:

CCI [redacted]

10.12.8.3. Safety Assessments

See Section 8.3.

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10.12.8.3.1. Stopping Rules for Substudy B

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

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

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

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

A stopping rule is met if either of the following rules occurs **within 4 weeks** after administration of study intervention.

Targeted Cardiac Abnormalities

1. If any participant vaccinated with tIRV or qIRV develops a suspected or confirmed diagnosis of myocarditis or pericarditis.

Death

2. If any participant vaccinated with tIRV or qIRV dies following administration of study intervention, irrespective of investigator assessment of relatedness.

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

See Section 8.4.

10.12.8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

10.12.8.6. Genetics

See Section 8.6.

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10.12.8.7. Biomarkers

Biomarkers are not evaluated in this study.

10.12.8.8. Immunogenicity Assessments

See Section 10.12.8.2.1.

10.12.8.9. Health Economics

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

10.12.8.10. Substudy B Procedures

10.12.8.10.1. Visit 201 – 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 their 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.

- Perform the VCT verification process, if applicable. This process helps ensure Pfizer clinical data quality and participant safety on trials by aiding investigational sites in the monitoring for and halting of dual enrollment of participants.
- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including age in years, sex, race, and ethnicity).
- 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.
- Record nonstudy vaccinations as described in Section 10.12.6.9.
- Record prior receipt of any mRNA vaccine (eg, mRNA-based COVID-19 vaccine), as described in Section 10.12.6.9.
- Record licensed influenza vaccine information, if received, as described in Section 10.12.6.9.

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- If applicable, discuss contraceptive use as described in Section 10.4.

On the day of and prior to study intervention administration:

- Measure the participant's oral temperature.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 10.12.5.5.
- Collect a blood sample (approximately 30 mL), before administration of study intervention, CCI [redacted]
- Obtain the participant's randomization number and study intervention allocation using the IRT system.
- 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.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute events. Record any acute reactions (including time of onset) in the participant's source documents, on the CRF, and via PSSA as applicable.
- Assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
- Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, or longer, until any ongoing symptoms are resolved, with Day 1 being the day of vaccination.
- Provide a measuring device to measure local reactions at the injection site, and a thermometer for recording daily temperatures during the e-diary period; provide instructions on their use.
- 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 (>20 measuring device units).

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  - Severe pain at the injection site.
  - Any severe systemic event.
- 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.
- Remind participants that study staff may contact them to obtain additional information on symptoms entered into the e-diary until the symptoms resolve.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.12.8.10.5).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.12.8.10.2. Visit 202 – 4-Week Follow-Up Visit (After Vaccination) – 28 to 35 Days After Visit 201

- Record AEs, MAEs, SAEs, and NDCMCs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 10.12.6.9.
- Record prohibited medication use as described in Section 10.12.6.9.1.
- If applicable, discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 30 mL [redacted]
- Review the participant's e-diary data and record assessment in the CRF. Assess compliance, record any medically attended events (including hospitalizations), and collect stop dates for any local reaction or systemic event ongoing since the 7-day follow-up period after vaccination. Document in the CRF.

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    - For any ongoing local reactions or systemic events, the site will follow up until resolution and document and record stop dates in the CRF.

- Collect the participant's e-diary or assist the participant with removing the study application from their own personal device.
- 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.
- 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.

10.12.8.10.3. Visit 203 – 6-Month Follow-Up Visit (After Vaccination) – 175 to 189 Days After Visit 201

- Record MAEs, SAEs, and NDCMCs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 10.12.6.9.
- Record prohibited medication use as described in Section 10.12.6.9.1.
- Collect a blood sample of approximately 30 mL [redacted]
- 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.

10.12.8.10.4. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.3.4.2), Grade 3 systemic event (Section 8.3.4.3), or fever ≥39.0°C (≥102.1°F) (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 (>40.0°C [>104.0°F]) (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.

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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.
- The investigator or appropriate designee confirmed severe reactogenicity assessment via medical records and/or telehealth assessment.

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.

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10.12.8.10.5. 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 28 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 via central laboratory (Note: In addition to central ECG interpretation, local ECG and troponin interpretation may be used to inform decision making necessary to ensure the immediate safety of participants.):

- ECG and
- Measurement of the troponin I 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.

10.12.9. Substudy B Statistical Considerations

10.12.9.1. Statistical Hypotheses

There are no statistical hypotheses in Substudy B.

10.12.9.1.1. Estimands

The estimands corresponding to the primary, secondary, CCI [redacted] objectives are described in the table in Section 10.12.3.

10.12.9.1.2. Multiplicity Adjustment

There is no multiplicity adjustment for Substudy B, as all analyses are descriptive in nature.

10.12.9.2. Analysis Sets

See Section 9.2 for defined analysis sets.

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10.12.9.3. Statistical Analyses

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

10.12.9.3.1. General Considerations

See Section 9 for general considerations of statistical analyses.

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

Endpoint	Statistical Analysis Methods
Safety	• Point estimates and the associated exact 2-sided 95% CIs for the proportion of participants reporting each event (local reactions, systemic events) for up to 7 days after vaccination calculated by the Clopper-Pearson method will be provided for each vaccine group. • Point estimates and the associated exact 2-sided 95% CIs for the proportion of participants reporting each AE through 4 weeks after vaccination calculated by the Clopper-Pearson method will be provided for each vaccine group. • Point estimates and the associated exact 2-sided 95% CIs for the proportion of participants reporting each event (SAEs, AEs, MAEs, NDCMCs) through 6 months after vaccination calculated by the Clopper-Pearson method will be provided for each vaccine group.

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

Endpoint	Statistical Analysis Methods
Immunogenicity (HAIs [redacted])	• HAI GMTs and associated 2-sided 95% CIs will be provided for each strain, by vaccine group, at baseline and 4 weeks after vaccination. • HAI GMFRs from before vaccination to 4 weeks after vaccination, and associated 2-sided 95% CIs, will be provided for each strain, by vaccine group. • The proportion of participants achieving HAI seroconversion at 4 weeks after vaccination, and associated 2-sided Clopper-Pearson 95% CIs, will be provided for each strain, by vaccine group.

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Endpoint	Statistical Analysis Methods
	• The proportion of participants with HAI titers ≥1:40 and associated 2-sided Clopper-Pearson 95% CIs will be provided for each strain, by vaccine group, at baseline and 4 weeks after vaccination.

10.12.9.3.4. CCI [redacted] Endpoint(s)

Endpoint	Statistical Analysis Methods
CCI [redacted]	The statistical methods used for the related endpoints will be defined in the study SAP.

10.12.9.3.5. Other Analyses

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis within 28 days after a study vaccination (ECG, troponin I level, cardiac echocardiogram, and/or cardiac magnetic resonance study) will be summarized and listed by vaccine group.

10.12.9.4. Interim Analyses

As the study is open-label to the sponsor, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, dose selection, and/or supporting clinical development.

10.12.9.5. Sample Size Determination

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

Approximately 90 participants will be enrolled for each vaccine group; therefore, a total of approximately up to 450 participants may be enrolled into this substudy.

For safety outcomes in the study, Table 8 shows the probability of observing at least 1 AE for a given true event rate of a particular AE with 90 participants in each vaccine group.

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Table 8. Probability of Observing at Least 1 AE by Assumed True Event Rate

Sample Size	Assumed True Rate of an AE	Probability of Observing at Least 1 AE
90	0.5%	36.3%
	1.0%	59.5%
	2.0%	83.8%
	5.0%	99.0%
	7.0%	99.9%

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10.13. Appendix 13: Substudy C

10.13.1. SoA – Substudy C

Visit Number	Screening	301	302[a]	303	304
Visit Description	Screening	Vaccination	1-Week Follow-Up Visit	4-Week Follow-Up Visit	6-Month Follow-Up Visit
Visit Window (Days)	0 to 28 Days Before Visit 301	Day 1	6 to 8 Days After Visit 301	28 to 35 Days After Visit 301	175 to 189 Days After Visit 301
Visit Type/Location	Site	Site	Site	Site	Site
Obtain informed consent	X				
Perform VCT verification process, if applicable	X				
Assign participant number	X				
Obtain demography and medical history	X				
Perform 12-lead triplicate ECG	X				
Perform physical examination[b]	X				
Collect blood sample for troponin I laboratory testing	~2.5 mL				
Collect nonstudy vaccine information	X	X	X	X	X
Collect information regarding last dose of prior licensed influenza vaccine, and prior receipt of any mRNA vaccine	X				
Collect prohibited medication use		X	X	X	X
Confirm use of contraceptives (if appropriate)	X	X	X	X	
Review troponin I and ECG results		X			
Perform clinical assessment[c]		X			
Measure vital signs (including body temperature)	X	X			
Confirm eligibility		X			
Review temporary delay criteria		X			
Collect blood sample [redacted]		~30 mL		~30 mL	~30 mL
Collect blood sample [redacted]		~[redacted] mL	~[redacted] mL		~[redacted] mL
Obtain randomization number and study intervention allocation		X			
Administer study intervention		X			

Visit Number	Screening	301	302[a]	303	304
Visit Description	**Screening**	**Vaccination**	**1-Week Follow-Up Visit**	**4-Week Follow-Up Visit**	**6-Month Follow-Up Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 301**	**Day 1**	**6 to 8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**175 to 189 Days After Visit 301**
Visit Type/Location	**Site**	**Site**	**Site**	**Site**	**Site**
Postvaccination observation (at least 30 minutes) and assessment of immediate events		X			
Explain reactogenicity e-diary completion, 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			
Site review of e-diary data with participant follow-up until ongoing event resolution, if applicable[d]		←	↔	→	
Collect AEs, MAEs, NDCMCs, and SAEs as appropriate[e]	X	X	X	X	X
Collect e-diary or assist the participant with deleting application				X	

a. Visit 302 will only be conducted for participants who have consented to provide the optional blood sample CCI [redacted]
b. Including measurement of weight and height at screening.
c. Including, if indicated, a physical examination.
d. Between visits, review the e-diary data online at frequent intervals. Contact the participant in order to obtain stop dates for any prespecified local reactions or systemic events. Assess any medically attended reactogenicity events (including hospitalizations) and e-diary compliance.
e. AEs are collected from the completion of informed consent to Visit 303. MAEs, NDCMCs, and SAEs are collected from the completion of informed consent to Visit 304 (approximately 6 months after vaccination). Additionally, any AEs occurring up to 48 hours after a blood draw must be recorded.

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10.13.2. Introduction (Substudy C)

10.13.2.1. Substudy C Rationale

CCI [redacted] This is particularly important for the older adults (≥65 years of age) who are at higher risk of influenza-related morbidity and mortality. The risk in the older adults (≥65 years of age) is further due to circulating A (H3N2) strains that rapidly mutate, leading to varying vaccine efficacy.[3,4,5,6] Substudy C is a Phase 1, randomized, active-controlled, observer-blinded (sponsor-unblinded) study to assess the safety, tolerability, CCI [redacted] of different doses of modRNA influenza vaccines in older adults (≥65 years of age) as listed below:

- tIRVs (separate LNPs for each strain) that contain CCI [redacted]:
  - tIRV3 – CCI [redacted]
  - tIRV4 – CCI [redacted]
  - tIRV5 – CCI [redacted]
  - tIRV6 – CCI [redacted]
  - tIRV7 – CCI [redacted]
  - tIRV8 – CCI [redacted]
- qIRV (separate LNPs for each strain) that contains 4 HA antigens encoding CCI [redacted]
  - qIRV3 (separate LNPs for each strain) – CCI [redacted]

This substudy will thereby inform the choice of the optimized influenza modRNA vaccine that may be further studied in older adults (≥65 years of age).

See Section 10.13.4 for more details regarding the design.

10.13.2.2. Background

See Section 2.2.

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10.13.2.3. Benefit/Risk Assessment

Besides those risks detailed in Section 2.7, the following additional risks are noted for Substudy C:

- The safety profile of modRNA vaccines containing CCI [redacted] is unknown. It is possible that modRNA vaccines containing CCI [redacted] components may have a different safety profile compared to modRNA vaccines containing HA alone.
- The maximum total dose of modRNA per vaccine in Substudy C is CCI [redacted] It is possible that vaccines containing higher doses of modRNA may have a different safety profile compared to vaccines containing lower doses of modRNA.
- The qIRV arm of Substudy C contains CCI [redacted]

The following measures will be put in place in order to mitigate these risks:

- Participants will be observed for at least 30 minutes after vaccination.
- Prompted reactogenicity will be recorded for 7 days (or until symptom resolution if still present 7 days after vaccination).
- AEs will be monitored from signing of the ICD to 4 weeks after vaccination, and MAEs/SAEs/NDCMCs will be collected for 6 months after vaccination.
- For all study intervention groups, safety data accumulated at least 72 hours after 10 participants have received study intervention in each group will be reviewed by the sponsor prior to enrollment of the remaining participants in each group.
- Review of safety data up to 1 week after vaccination of at least 20 participants in Groups 1C through 7C prior to the enrollment of Groups 8C and 9C (Table 9).
- Stopping rules will be monitored as per Section 10.13.8.3.1.

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10.13.3. Objectives, Endpoints, and Estimands (Substudy C)

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To define the safety and tolerability profile of tIRVs and qIRV in participants ≥65 years of age	• 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 • MAEs • NDCMCs	In participants receiving study intervention (safety population), the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs through 4 weeks after vaccination • MAEs through 6 months after vaccination • NDCMCs through 6 months after vaccination • SAEs through 6 months after vaccination
CCI [redacted]		

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Objectives	Endpoints	Estimands
CCI		

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10.13.4. Substudy C Design

10.13.4.1. Overall Design

This is a Phase 1, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, [redacted] of various formulations of tIRV (encoding HA [redacted], for the targeted seasonal strains [tIRV3 through tIRV8]) and qIRV3 [redacted]) compared to QIVs ([redacted] in healthy adults ≥65 years of age.

Up to approximately 270 participants ≥65 years of age will be enrolled and randomized to receive 1 dose of study intervention as shown in Table 9. Depending on the availability of study intervention and operational prioritization, study intervention groups may not all be randomized concurrently; however, a minimum of 2 groups will be open for randomization at any one time.

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Table 9. Number of Participants to Be Enrolled in Substudy C – Participants ≥65 Years of Age

Study Intervention Group	Study Intervention	Preformulated	Influenza Strains	CCI	Total modRNA Dose	Number of Participants
1C	QIV2	Yes	2023-2024 northern hemisphere seasonal strains Recommended by WHO for CCI influenza vaccines		N/A	30
2C	QIV3	Yes	2023-2024 northern hemisphere seasonal strains Recommended by WHO for CCI influenza vaccines		N/A	30
3C	tIRV3	No	A/H1N1 A/H3N2 B/Victoria		CCI	30
4C	tIRV4	No	A/H1N1 A/H3N2 B/Victoria			30
5C	qIRV3	No	CCI			30
6C	tIRV5	No	A/H1N1 A/H3N2 B/Victoria			30
7C	tIRV6	No	A/H1N1 A/H3N2 B/Victoria			30
8C	tIRV7	No	A/H1N1 A/H3N2 B/Victoria			30

Table 9. Number of Participants to Be Enrolled in Substudy C – Participants ≥65 Years of Age

Study Intervention Group	Study Intervention	Preformulated	Influenza Strains	CCI	Total modRNA Dose	Number of Participants
9C	tIRV8	No	A/H1N1	[redacted]	CCI [redacted]	30
			A/H3N2			
			B/Victoria			

a. CCI [redacted]

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Study intervention groups in which participants receive QIV2, QIV3, or modRNA doses up to CCI will initially be enrolled as detailed in Table 10. Safety data accumulated at least 7 days following vaccination of at least 20 participants in these groups will be reviewed by the sponsor and, if it is deemed acceptable, participants will be enrolled into study intervention groups in which they will receive modRNA doses up to CCI

For all study intervention groups:

- Enrollment will be controlled such that no more than 10 participants per group can be vaccinated on the first day. Safety data accumulated at least 72 hours after 10 participants have received study intervention in each group will be reviewed by the sponsor and vaccination of the remaining participants in each group will commence in a staggered manner if these data raise no safety concerns as shown in Table 10.

- Stopping rules will apply as detailed in Section 10.13.8.3.1.

See Table 10 for an overview of enrollment progression in Substudy C.

Blood samples of approximately 30 mL will be collected CCI prior to vaccination and at 4 weeks and 6 months after vaccination. Additional blood samples will be collected as summarized below:

- Approximately CCI mL of blood will be collected from participants (approximately 20 participants per group) who consent to this at the time points specified in Section 10.13.1 CCI

- Approximately 2.5 mL of blood will be collected from all participants at screening for assessment of troponin I.

Local reaction and systemic event data will be collected in an e-diary during the 7-day follow-up period, or longer for ongoing symptoms, after study vaccination (ie, from Day 1, the day of vaccination, until event resolution).

All AEs will be collected from informed consent signing through 4 weeks following vaccination. A subset of AEs (NDCMCs, MAEs, 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 will be collected.

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Table 10. Progression of Substudy C Enrollment

Study Intervention Group	Study Intervention	Total modRNA Dose	Enrollment						
			Active	Paused	Active	Paused	Active	Paused	Active
1C	QIV2	N/A	10	Safety review	20	Safety review	-	Safety review	-
2C	QIV3	N/A	10		20		-		-
3C	tIRV3	CCI	10	72 Hours' safety data	10	7 Days' safety data	5	72 Hours' safety data	5
4C	tIRV4		10		10		5		5
5C	qIRV3		-		10		10		10
6C	tIRV5		-		10		10		10
7C	tIRV6		-		10		10		10
8C	tIRV7		-		-		10		20
9C	tIRV8		-		-		10		20

10.13.4.2. Scientific Rationale for Study Design

See Section 2.1.

10.13.4.3. Justification for Dose

See Section 4.3.

10.13.4.4. End of Substudy Definition

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

A participant is considered to have completed the substudy if they have completed the last visit (Visit 304).

10.13.5. Substudy C Population

10.13.5.1. Substudy C Inclusion Criteria

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

Age and Sex:

1. Participants ≥65 years of age at Visit 301 (Day 1).

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Disease Characteristics:

Not applicable.

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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 10.10.

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. Receipt of licensed influenza vaccination for the 2023-2024 northern hemisphere season ≥6 months (≥180 days) before study intervention administration.

6. Has a BMI between 18 and 35 (inclusive) kg/m^2 on Day 1.

10.13.5.2. Substudy C Exclusion Criteria

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

Medical Conditions:

1. Diagnosed with influenza by an FDA-approved testing method ≤180 days before study intervention administration.

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. Any 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.

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6. Prior history of heart disease of concern: history of myocarditis, pericarditis, cardiomyopathy, coronary artery disease (including history of myocardial infarction, unstable angina), NYHA Class III and above heart failure, or significant arrhythmias.

   Note: Controlled hypertension is not exclusionary. "Controlled" is defined as hypertension not requiring significant change in therapy or hospitalization for worsening hypertension during the 6 weeks before enrollment.

Prior/Concomitant Therapy:

7. Receipt of chronic medications with known systemic immunosuppressant effects (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before enrollment.

   Note: Systemic corticosteroids when 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 meet this criterion. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

9. Any participant who has received investigational or licensed influenza vaccination <6 months (<180 days) before study intervention administration.

10. Receipt of chronic antiviral therapy with activity against influenza.

Prior/Concurrent Clinical Study Experience:

11. Participation in other studies involving administration of an investigational product within 28 days prior to, and/or during, participation in this study. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

12. Abnormal troponin I value at screening.

Other Exclusion Criteria:

13. 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.

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14. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results, as judged by the investigator, and/or is consistent with probable or possible myocarditis or pericarditis. Participants with a screening 12-lead ECG that shows an average QTcF >450 ms, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias should be excluded from study participation.

10.13.5.3. Lifestyle Considerations

See Section 5.3.

10.13.5.4. Screen Failures

See Section 5.4.

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

The following conditions may allow a participant to be enrolled once the conditions have resolved and the participant is otherwise eligible:

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 28 days before study intervention administration at Visit 301.

3. Anticipated receipt of any nonstudy vaccine within 28 days after study intervention administration at Visit 301.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration at Visit 301 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.

10.13.6. Substudy C Intervention and Concomitant Therapy

10.13.6.1. Study Intervention(s) Administered

Intervention Name	**tIRV**	**qIRV3**	**QIV2** (CCI [redacted]	**QIV3** CCI [redacted]
Type	Vaccine	Vaccine	Vaccine	Vaccine
Use	Experimental	Experimental	Comparator	Comparator
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP
Dose Formulation	Solution for injection	Solution for injection	Solution for injection	Solution for injection

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Intervention Name	tIRV	qIRV3	QIV2 (CCI)	QIV3 CCI
modRNA Unit Dose Strength(s)	tIRV3: CCI tIRV4: tIRV5: tIRV6: tIRV7: tIRV8:	CCI	N/A	N/A
Targeted Influenza Strains	As recommended by WHO for CCI vaccines (2023-2024 northern hemisphere influenza season)[1], ie, CCI	CCI	As recommended by WHO for CCI vaccines (2023-2024 northern hemisphere influenza season)	As recommended by WHO for CCI vaccines (2023-2024 northern hemisphere influenza season)
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Sourcing	tIRV 3 and tIRV4: mIRVs encoding CCI will be mixed at the site to generate tIRV at the relevant dose-level combination. Please see the IPM for further details. tIRV5, tIRV6, tIRV7, and tIRV8: mIRVs encoding CCI will be mixed at the site to generate tIRV at the relevant dose-level combination. Please see the IPM for further details.	mIRVs encoding CCI will be mixed at the site to generate qIRV3 at the relevant dose-level combination. Please see the IPM for further details.	Provided centrally by the sponsor	Provided centrally by the sponsor
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 in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided either as a PFS or in a glass vial as open-label supply. Each PFS/vial will be labeled as required per country requirement.	Study intervention will be provided either as a PFS or in a glass vial as open-label supply. Each PFS/vial will be labeled as required per country requirement.
SRSD	IB	IB	CCI USPI	CCI USPI

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10.13.6.1.1. Administration

Participants will receive 1 dose of study intervention at Visit 301 in accordance with the study's SoA (Section 10.13.1). Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm. Study intervention will be administered by an **unblinded** administrator.

10.13.6.2. Preparation, Handling, Storage, and Accountability

See Section 6.2.

10.13.6.3. Assignment to Study Intervention

See Section 6.3.

10.13.6.4. Blinding

10.13.6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

10.13.6.4.2. 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 the study interventions, these will be administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

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

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

10.13.6.4.3. Blinding of the Sponsor

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

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10.13.6.4.4. 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 vaccine 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 vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

10.13.6.5. Study Intervention Compliance

See Section 6.5.

10.13.6.6. Dose Modification

Not applicable.

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

See Section 6.7.

10.13.6.8. Treatment of Overdose

See Section 6.8.

10.13.6.9. Prior and Concomitant Therapy

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Section 10.4).

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

- Any vaccinations received from 28 days prior to study enrollment until the last visit (Visit 304).
- Last dose of licensed influenza vaccine.
- Prior receipt of any mRNA vaccine (eg, mRNA-based COVID-19 vaccine).
- Prohibited medications listed in Section 10.13.6.9.1, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

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10.13.6.9.1. 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 7.2). Medications should not be withheld if required for a participant's medical care.

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after study vaccination at Visit 301.
- Receipt of any mRNA vaccine within 28 days before and 28 days after study vaccination at Visit 301.
- Receipt of any other (nonstudy) seasonal influenza vaccine after study intervention administration through completion of the study.
- Receipt of chronic medications with known systemic immunosuppressant effects, or radiotherapy, within 60 days before enrollment through conclusion of the study.
- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 60 days prior to enrollment through 28 days after administration of the study intervention.

  Note: Receipt of short term (<14 days) systemic corticosteroids at a dose of ≥20 mg/day of prednisone or equivalent is prohibited from enrollment through 28 days after administration of study intervention.
- Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.
- 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.

10.13.6.9.2. Permitted During the Study

- Medication other than that described as prohibited in Section 10.13.6.9.1 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.

10.13.7. Discontinuation of Substudy C Intervention and Participant Discontinuation/Withdrawal

See Section 7.

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10.13.8. Substudy C Assessments and Procedures

10.13.8.1. Administrative and Baseline Procedures

See Section 8.1.

The minimal blood sampling volume for individual participants in this study is approximately 92.5 mL (2.5 mL at screening, and 30 mL at Visits 301, 303, and 304). An additional optional blood sample of CCI mL will be collected from all participants at the time points specified in Section 10.13.1 CCI
(CCI mL at Visits 301, 302, and 304).

CCI

10.13.8.3. Safety Assessments

See Section 8.3.

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10.13.8.3.1. Stopping Rules for Substudy C

The following stopping rules are in place for all participants in Substudy C receiving tIRV or qIRV based on review of AEs and e-diary reactogenicity. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor study team in order to promptly identify and flag any event that potentially contributes to a stopping rule.

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

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

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

A stopping rule is met if any of the following rules occur **within 4 weeks** after administration of study intervention. E-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

Stopping Rule Criteria:

Targeted Cardiac Abnormalities

1. If any participant vaccinated with tIRV or qIRV develops a suspected or confirmed diagnosis of myocarditis or pericarditis.

Death

2. If any participant vaccinated with tIRV or qIRV dies following administration of study intervention, irrespective of investigator assessment of relatedness.

AEs and SAEs, Including Reactogenicity Events

3. If any of the following occur after vaccination in the same tIRV or qIRV group:
    - Any participant experiences an SAE of any severity assessed as related by the investigator.
    - ≥2 Participants develop the same or similar Grade 3 prompted AE (as collected in the reactogenicity e-diary and confirmed by the investigator) sustained for over 24 hours.

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- ≥2 Participants develop the same or similar Grade 3 or higher unprompted AE assessed as related to study intervention by the investigator. The following events are excluded from this criterion:

  a. Myocarditis/pericarditis (see Targeted Cardiac Abnormalities above)

- ≥2 Participants develop the same investigator-confirmed fever >38.9°C to 40.0°C (102.1°F-104.0°F) sustained for over 24 hours.

- Any participant develops an investigator-confirmed Grade 4 local or systemic prompted AE or fever >40.0°C (>104.0°F).

Notes:

- Stopping rule criteria exclude events confirmed by the investigator as having been entered in the e-diary in error by the participant.
- The grading scales utilized for the stopping rules for local reactions and systemic events are detailed in Section 8.3.4.1. The grading scales for AEs are detailed in Section 10.3.3.
- "Prompted AEs" refers to local reactions, systemic events, and fever.
- "Unprompted AEs" refers to any other events.

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

See Section 8.4.

10.13.8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

10.13.8.6. Genetics

See Section 8.6.

10.13.8.7. Biomarkers

Biomarkers are not evaluated in this study.

CCI [redacted]

10.13.8.9. Health Economics

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

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10.13.8.10. Substudy C Procedures

10.13.8.10.1. Screening (0 to 28 Days Before Visit 301)

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 their 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.

- Perform the VCT verification process, if applicable. This process helps ensure Pfizer clinical data quality and participant safety in trials by aiding investigational sites in the monitoring for and halting of dual enrollment of participants.
- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including age in years, sex, race, and ethnicity).
- Obtain any medical history of clinical significance.
- Perform 12-lead triplicate ECG.
- Perform physical examination, including vital signs (weight, height, oral temperature, pulse rate, and seated BP), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample of approximately 2.5 mL, as detailed in the laboratory manual, for troponin I laboratory testing.
- Record nonstudy vaccinations as described in Section 10.13.6.9.
- Record prior receipt of any mRNA vaccine (eg, mRNA-based COVID-19 vaccine), as described in Section 10.13.6.9.
- Record licensed influenza vaccine information, if received, as described in Section 10.13.6.9.
- If applicable, discuss contraceptive use as described in Section 10.4.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (based on available information).
- Record AEs as described in Section 8.4.

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- The investigator or an authorized designee completes the CRF.

10.13.8.10.2. Visit 301 – Vaccination (Day 1)

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

- Record MAEs, SAEs, NDCMCs, and AEs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 10.13.6.9.
- Record prohibited medication use as described in Section 10.13.6.9.1.
- If applicable, discuss contraceptive use as described in Section 10.4.
- Review screening laboratory troponin I and ECG results.
- 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.

On the day of and prior to study intervention administration:

- On the day of and prior to study intervention administration, measure vital signs, including oral temperature, pulse rate, and seated BP.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 10.13.5.5.
- Collect a blood sample (approximately 30 mL), before administration of study intervention, CCI [redacted]
- For participants who provide consent to do so, collect a blood sample (approximately 100 mL), before administration of study intervention, CCI [redacted]
- Obtain the participant's randomization number and study intervention allocation using the IRT system.
- 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.

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

- Assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.

- Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, or longer, until any ongoing symptoms are resolved, with Day 1 being the day of vaccination.

- Provide a measuring device to measure local reactions at the injection site, and a thermometer for recording daily temperatures during the e-diary period; provide instructions on their use.

- 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 (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

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

- Remind participants that study staff may contact them to obtain additional information on symptoms entered into the e-diary until the symptoms resolve.

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.13.8.10.7).

- 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.

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

10.13.8.10.3. Visit 302 – 1-Week Follow-Up Visit (After Vaccination) – 6 to 8 Days After Visit 301

Visit 302 will only be conducted for participants who have consented to provide the optional blood sample [redacted]

- Record AEs, MAEs, SAEs, and NDCMCs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 10.13.6.9.
- Record prohibited medication use as described in Section 10.13.6.9.1.
- If applicable, discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 100 mL) [redacted]
- If the participant has completed the e-diary period, review the participant's e-diary data and record assessment in the CRF. Assess compliance, record any medically attended events (including hospitalizations), and collect stop dates for any local reactions or systemic events ongoing since the 7-day follow-up period after vaccination. Document in the CRF.
    - For any ongoing local reactions or systemic events, the site will follow up until resolution and document and record stop dates in the CRF.
- 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 (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
    - Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

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- Remind participants that study staff may contact them to obtain additional information on symptoms entered into the e-diary until the symptoms resolve.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.13.8.10.7).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.13.8.10.4. Visit 303 – 4-Week Follow-Up Visit (After Vaccination) – 28 to 35 Days After Visit 301

- Record AEs, MAEs, SAEs, and NDCMCs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 10.13.6.9.
- Record prohibited medication use as described in Section 10.13.6.9.1.
- If applicable, discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 30 mL [redacted]
- Review the participant's e-diary data and record the assessment in the CRF. Assess compliance, record any medically attended events (including hospitalizations), and collect stop dates for any local reaction or systemic event ongoing since the 7-day follow-up period after vaccination. Document in the CRF.
  - For any ongoing local reactions or systemic events, the site will follow up until resolution and document and record stop dates in the CRF.
- Collect the participant's e-diary or assist the participant with removing the study application from their own personal device.
- 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.
- 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.

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10.13.8.10.5. Visit 304 – 6-Month Follow-Up Visit (After Vaccination) – 175 to 189 Days After Visit 301

- Record MAEs, SAEs, and NDCMCs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 10.13.6.9.
- Record prohibited medication use as described in Section 10.13.6.9.1.
- Collect a blood sample of approximately 30 mL CCI [redacted]
- For participants who provide consent to do so, collect a blood sample (approximately 100 mL) CCI [redacted]
- 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.

10.13.8.10.6. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.3.4.2), Grade 3 systemic event (Section 8.3.4.3), or fever ≥39.0°C (≥102.1°F) (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 >40.0°C (>104.0°F) (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.
- The investigator or appropriate designee confirmed severe reactogenicity assessment via medical records and/or telehealth assessment.

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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.

10.13.8.10.7. 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 28 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 via central laboratory (Note: In addition to central ECG interpretation, local ECG and troponin interpretation may be used to inform decision making necessary to ensure the immediate safety of participants.):

- ECG and
- Measurement of the troponin I level

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

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- 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.

10.13.9. Substudy C Statistical Considerations

10.13.9.1. Statistical Hypotheses

There are no statistical hypotheses in Substudy C.

10.13.9.1.1. Estimands

The estimands corresponding to the primary CCI [redacted] objectives are described in the table in Section 10.13.3.

10.13.9.1.2. Multiplicity Adjustment

There is no multiplicity adjustment for Substudy C, as all analyses are descriptive in nature.

10.13.9.2. Analysis Sets

See Section 9.2 for defined analysis sets.

10.13.9.3. Statistical Analyses

The SAP will be developed and finalized for this substudy 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 CCI [redacted] endpoints.

10.13.9.3.1. General Considerations

See Section 9 for general considerations of statistical analyses.

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

Endpoint	Statistical Analysis Methods
Safety	• Point estimates and the associated exact 2-sided 95% CIs for the proportion of participants reporting each event (local reactions, systemic events) for up to 7 days after vaccination calculated by the Clopper-Pearson method will be provided for each vaccine group.

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Endpoint	Statistical Analysis Methods
	• Point estimates and the associated exact 2-sided 95% CIs for the proportion of participants reporting each AE through 4 weeks after vaccination calculated by the Clopper-Pearson method will be provided for each vaccine group. • Point estimates and the associated exact 2-sided 95% CIs for the proportion of participants reporting each event (AEs, SAEs, MAEs, NDCMCs) through 6 months after vaccination calculated by the Clopper-Pearson method will be provided for each vaccine group.

10.13.9.3.3. CCI [redacted] Endpoint(s)

Endpoint	Statistical Analysis Methods
CCI [redacted] CCI [redacted]	CCI [redacted]
CCI [redacted]	The statistical methods used for the related endpoints will be defined in the study SAP.
CCI [redacted] CCI [redacted]	The statistical methods used for the related endpoints will be defined in the study SAP.

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10.13.9.3.4. Other Analyses

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis within 28 days after a study vaccination (ECG, troponin I level, cardiac echocardiogram, and/or cardiac magnetic resonance study) will be summarized and listed by vaccine group.

10.13.9.4. Interim Analyses

As the study is open-label to the sponsor, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, dose selection, and/or supporting clinical development.

10.13.9.5. Sample Size Determination

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

Approximately 30 participants will be enrolled for each vaccine group; therefore, a total of approximately 270 participants may be enrolled into this substudy.

For safety outcomes in the study, Table 11 shows the probability of observing at least 1 AE for a given true event rate of a particular AE with 30 participants in each vaccine group.

Table 11. Probability of Observing at Least 1 AE by Assumed True Event Rate

Sample Size	Assumed True Rate of an AE	Probability of Observing at Least 1 AE
30	0.5%	14.0%
	1.0%	26.0%
	2.0%	45.5%
	5.0%	78.5%
	7.0%	88.7%

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10.14. Appendix 14: Abbreviations

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

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
ADE	adverse device effect
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
CCI	
bIRV	bivalent influenza modRNA vaccine
BLQ	below the limit of quantitation
BMI	body mass index
BNT162b2	Pfizer-BioNTech COVID-19 vaccine
BP	blood pressure
CBER	Center for Biologics Evaluation and Research (United States)
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations (United States)
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
CTIS	Clinical Trial Information System
DCT	data collection tool
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding

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Abbreviation	Term
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eICD	electronic informed consent document
CCI [redacted]	
eGFR	estimated glomerular filtration rate
eSAE	electronic safety adverse event
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
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
CCI [redacted]	
HIV	human immunodeficiency virus
CCI [redacted]	
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
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	Internet Protocol
IPAL	investigational product accountability log
IPM	investigational product manual
IRB	institutional review board
IRT	interactive response technology
IRV	influenza modRNA vaccine

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Abbreviation	Term
ISO	International Organization for Standardization
IV	intravenous(ly)
KDIGO	Kidney Disease: Improving Global Outcomes
LAIV	live attenuated influenza vaccine
LBBB	left bundle branch block
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MDR	Medical Device Regulation
MAE	medically attended adverse event
mIRV	monovalent influenza modRNA vaccine
mITT	modified intent-to-treat
CCI [redacted]	
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
mRNA	messenger ribonucleic acid
mRNA-1273	Moderna's COVID-19 vaccine
CCI [redacted]	
N/A	not applicable
CCI [redacted]	
NDCMC	newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product
NYHA	New York Heart Association
PACL	protocol administrative change letter
CCI [redacted]	
PFS	prefilled syringe
PI	principal investigator
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QTc	corrected QT interval
QTcF	QT interval corrected by the Fridericia formula
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SAE	serious adverse event
SADE	serious adverse device effect
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

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Abbreviation	Term
Screat	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SSA	Substudy A
SSB	Substudy B
SUSAR	suspected unexpected serious adverse reaction
T bili	total bilirubin
CCI	
tIRV	trivalent influenza modRNA vaccine
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States package insert
VCT	Verified Clinical Trials
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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