A STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RESPIRATORY COMBINATION VACCINE CANDIDATES IN OLDER ADULTS

Study Intervention Number:	PF-07941314
Study Intervention Name:	RSV Subunit and Influenza modRNA Combination Vaccine
US IND Number:	Not applicable
EudraCT Number:	Not applicable
ClinicalTrials.gov ID:	NCT05788237
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5401001
Phase:	1b

Brief Title: A Safety, Tolerability, and Immunogenicity Study of Respiratory Combination Vaccine Candidates in Older Adults

Document History

Document	Version Date
Amendment 1	30 May 2023
Original protocol	20 Dec 2022

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 1 (30 May 2023)

Overall Rationale for the Amendment:

Substudy B will investigate 2 formulations of RSVpreF + qIRV of differing volumes and osmolarities. These formulations will be evaluated for safety, tolerability, and immunogenicity, with the goal of selecting a formulation for further study.

Section # and Name or Page Number	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1.2 Section 1.3.2 Section 10.10 Appendix 10	Added information specific to Substudy B.	Substudy B will evaluate the safety and immunogenicity of combination RSVpreF + qIRV in a 1.0-mL volume compared to RSVpreF + qIRV in a 0.5-mL volume.	Substantial
Section 1.1.1.2 Overall Design, Section 10.9.4.1 Substudy A Rationale, and Section 10.9.6.1 Overall Design	Changed "multicenter" to "single-center."	The study design changed from multicenter to single center after protocol finalization but prior to study start.	Nonsubstantial
Section 1.1.1.3 Section 10.9.6.1	Definition of *enrolled* modified.	Alignment with the SAP.	Substantial
Section 2.1	Revised the study rationale to address the addition of Substudy B.	Substudy B added to protocol.	Substantial
Section 2.2.3.1	Updated the Clinical Overview.	Modified C3671006 participant numbers and added the immunogenicity results.	Substantial

Section # and Name or Page Number	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 2.2.3.2	Added the results for Study C4781001. The number of participants dosed with qIRV in the C4781004 study has been added. Also added that an independent data review committee has endorsed continuation of the C4781004 study as of May 2023.	Results availability for C4781001. Study status for C4781004 as of May 2023.	Substantial
Section 2.3.1	Updated first and last table rows to reflect new information in qIRV exposures.	C4781004 qIRV safety updates are available.	Substantial
Section 2.3.3	Added risks and benefits applicable to Substudy B.	Mandatory safety requirement.	Substantial
Section 6.1.1	Updated study interventions.	Added details applicable to Substudy B and clarified those interventions only applicable to Substudy A.	Substantial
Section 8.1.1	Removed first bullet point.	Not applicable to either substudy.	Nonsubstantial
Section 8.3.5	Added pregnancy testing requirements.	Women of childbearing potential will be recruited in Substudy B.	Substantial
Throughout Document	1. "See Section" cross-references have been added. 2. Applied associations by substudy.	1. These refer the reader to the location of specific sections of text applicable by substudy. 2. The addition of Substudy B required a revision.	Nonsubstantial for both
Section 8.3.2.1 Blood Pressure and Pulse Rate	Revised the section to include the study time point that will require measurement of participant pulse rate and seated blood pressure.	The addition of Substudy B required a revision to this section to incorporate relevant cross-reference to Substudy A and Substudy B.	Substantial
Section 8.4.8, bullet 3	Modified AESI statement in relation to study vaccination.	The addition of Substudy B required a revision to this section.	Substantial

Section # and Name or Page Number	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 9.3.1	Added statement that related e-diary data may be included in the analysis.	To align with the SAP.	Substantial
Section 10.1.6 - Data Sharing	Modified statement that data sharing will become available in 18 months, rather than 24 months.	Template update.	Nonsubstantial
Section 10.1.9	Study start date definition changed.	Template update.	Nonsubstantial
Section 10.2 Appendix 2: Clinical Laboratory Tests	Added a statement to indicate that routine clinical laboratory tests are not applicable to Substudy B.	The addition of Substudy B required a revision to this section.	Substantial
Section 10.4.2.1 and Section 10.4.2.2	Added contraceptive requirements for women of childbearing potential.	Women of childbearing potential will be recruited in Substudy B.	Substantial
Table 7, Table 8, Table 9	Added SoA Substudy B as Table 7. Updated table numbering.	Formatting correction.	Nonsubstantial
Section 10.9.5 and Section 10.9.11.3.2	Two exploratory estimands related to Substudy A HAI analyses have been deleted.	Modifications to the SAP.	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

A Study to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Combination Vaccine Candidates in Older Adults

Brief Title

A Safety, Tolerability, and Immunogenicity Study of Respiratory Combination Vaccine Candidates in Older Adults

Regulatory Agency Identification Number(s):

US IND Number:	Not applicable
EudraCT Number:	Not applicable
ClinicalTrials.gov ID:	NCT05788237
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5401001
Phase:	1b

Rationale

The cocirculation of RSV and influenza significantly impacts the older adult population, where there is a higher incidence of respiratory infections and increased morbidity and mortality during the winter months. In the early 2022-2023 US winter, the incidences of influenza and RSV-related disease were increasing. As vaccines against influenza and COVID-19 can be administered at a single healthcare visit as individual vaccinations, requiring multiple injections, should a licensed RSV vaccine become available, the coadministration of these vaccines would likely occur at the same time of year. The Pfizer RSV vaccine, RSVpreF, was recently found to be efficacious against RSV-associated LRTI in older adults. Concurrent administration of vaccines against these respiratory viral infections reduces the need for multiple healthcare or pharmacy visits and may improve vaccine uptake. A combination vaccine with RSVpreF and qIRV would require 1 injection at a healthcare provider visit. A study of combined vaccination is required to investigate potential immunological interference in addition to safety and tolerability. Pfizer is currently investigating the efficacy of a quadrivalent modified RNA (modRNA) influenza vaccine candidate (qIRV). This study series will investigate the administration of combined RSVpreF with qIRV to assess the safety, tolerability, and potential for immunological interference.

1.1.1. Substudy A

The first of the combination RSVpreF + qIRV vaccine studies will be conducted as a Phase 1b substudy in healthy participants ≥60 years of age. CCI [redacted]

1.1.1.1. Objectives, Endpoints, and Estimands

Please refer to the appendices for the objectives, endpoints, and estimands for each substudy.

Substudy A

Objectives	Endpoints	Estimands
Primary Safety	**Primary Safety**	**Primary Safety**
• To evaluate the safety profile of combination RSVpreF + qIRV	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions within 7 days following each vaccination • Systemic events within 7 days following each vaccination • AEs within 1 month after each vaccination • SAEs throughout the study
Primary Immunogenicity	**Primary Immunogenicity**	**Primary Immunogenicity**
• To describe the immune responses elicited by combination RSVpreF + qIRV in comparison with those elicited by RSVpreF alone	• RSV A and RSV B NTs	In participants in compliance with the key protocol criteria (evaluable participants): • GMR of NTs for each RSV subgroup (A or B) 1 month after vaccination with combination RSVpreF + qIRV to that with RSVpreF alone (sequential-administration group, Visit A103)
• To describe the immune responses elicited by combination RSVpreF + qIRV in comparison with those elicited by qIRV alone	• Strain-specific HAI titers for the current seasonal strains (2×A, 2×B) recommended by WHO for recombinant or cell-based influenza vaccines	In participants in compliance with the key protocol criteria (evaluable participants): • GMR of strain-specific HAI titers 1 month after vaccination with combination RSVpreF + qIRV to that with qIRV alone (sequential-administration group, Visit A102)

1.1.1.2. Overall Design

Substudy A will be conducted as a Phase 1b, single-site, parallel-group, randomized, placebo-controlled, observer-blinded substudy of RSVpreF and a nucleoside-modified RNA vaccine (qIRV) against RSV and influenza when administered as a combined vaccine and when administered alone.

Healthy adults ≥60 years of age will be randomized 1:1 to either Group 1: combination (RSVpreF + qIRV) (Visit A101) followed by placebo (Visit A102); or Group 2: sequential administration of qIRV (Visit A101) followed by RSVpreF (Visit A102) administered 1 month apart. Randomization will be stratified by 3 age groups (60-64, 65-79, and ≥80 years) within the study site. Study groups, blood draws, and safety assessment timings are presented below.

Substudy A Design

Healthy adults ≥60 years of age (125 per group, randomized 1:1)	**Visit A101 (Day 1)** **Vaccination 1**	**Visit A102 (Month 1)** 28-35 days after Vaccination 1 **Vaccination 2**	**Visit A103 (Month 2)** 28-35 days after Vaccination 2 **Follow-up**
STUDY GROUPS			
Group 1: Combination RSVpreF + qIRV / placebo	Combination (RSVpreF + qIRV) 	Placebo 	Blood draw 
Group 2: Sequential administration qIRV / RSVpreF	qIRV 	RSVpreF 	Blood draw 
SAFETY			
Local reactions and systemic events	Days 1 through 7 	Days 1 through 7 	
AEs and AESIs	Consent through study completion		 48 hours
SAEs	Consent through study completion		

1.1.1.3. Number of Participants

Approximately 250 healthy participants (n=125 per group) will be enrolled in Substudy A. Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process.

1.1.1.4. Study Population

Substudy A

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into Substudy A:

Age and Sex:

1. Participants ≥60 years of age at study enrollment.

- Refer to Section 10.4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

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

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

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.10.

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

5. Receipt of licensed influenza vaccination for the 2022-2023 northern hemisphere season or 2022 southern hemisphere season >120 days before study intervention administration.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

Medical Conditions

1. A confirmed diagnosis of RSV infection or influenza ≤120 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. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate IM injection.

4. Serious chronic disorder, including metastatic malignancy, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excludes the participant from participating in the study.

5. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy

6. Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before study intervention administration, or planned receipt throughout the study.

Note: Systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent (eg, for cancer or an autoimmune disease) or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

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

8. Receipt of any licensed RSV vaccine at any time prior to enrollment, or planned receipt throughout the study.

9. Receipt of any licensed influenza vaccine ≤120 days before study enrollment, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience

10. Participation in other studies involving an investigational RSV vaccine or mRNA influenza vaccine at any time prior to enrollment, and thereafter until study completion, regardless of vaccine assignment.

11. Participation in any other interventional studies within 28 days before study enrollment through study completion. 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.

1.1.1.5. Study Arms and Duration

Substudy A

For individual participants, the duration of Substudy A is about 2 months. Based on an estimated 2-month enrollment period, the duration of Substudy A will be approximately 4 months.

Study Interventions for Substudy A

Substudy A
Group 1: Combination (RSVpreF + qIRV) / Placebo

Intervention Name	Vaccination 1 Combination (RSVpreF + qIRV)		Vaccination 2 Placebo
Vaccine Component	RSVpreF 2 Stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B	qIRV Encoding HA of 4 strains as recommended for the influenza season (2 A strains and 2 B strains)	Placebo
Dose Formulation	RSV vaccine 120 µg/vial powder for solution for injection	Quadrivalent influenza suspension for injection, CCI mg/mL (qIRV)	0.9% Normal saline
Product for Reconstitution	Sterile water as diluent for injection (0.65 mL/syringe)	N/A	N/A
Unit Dose Strength(s)	120 µg	CCI µg	0.5 mL

Substudy A

Group 1: Combination (RSVpreF + qIRV) / Placebo

Intervention Name	Vaccination 1 Combination (RSVpreF + qIRV)	Vaccination 2 Placebo
Route of Administration	After combining both vaccines, a single 1-mL IM injection is given into the deltoid muscle of the nondominant arm (preferred).	0.5-mL IM injection into the deltoid muscle of the nondominant arm (preferred)
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by Pfizer	Provided centrally by Pfizer
Packaging and Labeling	**RSVpreF** is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. It is reconstituted with a PFS of sterile water diluent for injection (supplied). **qIRV** is supplied as CCI [redacted] Study intervention(s) will be labeled as per country requirements.	Study intervention will be supplied in a glass or plastic vial. Each vial will be labeled as per country requirements.

Substudy A

Group 2: Sequential Administration qIRV / RSVpreF

Intervention Name	Vaccination 1 qIRV	Vaccination 2 RSVpreF
Vaccine Component	qIRV qIRV, ie, encoding HA of 4 strains as recommended for the influenza season (2 A strains and 2 B strains)	RSVpreF 2 Stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B Sterile water as diluent for injection
Dose Formulation	Quadrivalent influenza suspension for injection, CCI mg/mL (qIRV)	RSV vaccine 120 µg/vial powder for solution for injection
Product for Reconstitution	N/A	Sterile water as diluent for injection (0.65 mL/syringe)
Unit Dose Strength(s)	CCI µg	120 µg
Route of Administration	0.5-mL IM injection into the deltoid muscle of the nondominant arm (preferred)	0.5-mL IM injection into the deltoid muscle of the nondominant arm (preferred)
Use	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by Pfizer	Provided centrally by Pfizer
Packaging and Labeling	qIRV is supplied as CCI Study intervention(s) will be labeled as per country requirements.	RSVpreF is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial. It is reconstituted with a PFS of sterile water diluent for injection (supplied). Study intervention(s) will be labeled as per country requirements.

1.1.1.6. Statistical Methods

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

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

The primary immunogenicity objectives will be evaluated descriptively by the ratio of the GMT for the combination vaccine to the GMT for the individual vaccine for RSV subgroup A and subgroup B NTs and strain-specific HAI NTs.

1.1.2. Substudy B

The development of [CCI] is sometimes required for injectable products to demonstrate efficacy, safety, [CCI] The benefits obtained [CCI] need to be balanced against the potential risks to tolerability. [CCI]

The formulation development of combination vaccines requires consideration of [CCI] to determine whether the ultimate product achieves the desired effects in a safe and tolerable manner. [CCI]. A prior study of healthy adults 18 to 40 years of age who received anterolateral thigh injection with 5 suspensions containing the same components as excipients of a combined pertussis–inactivated poliomyelitis–*Haemophilus influenzae* type b pediatric vaccine investigated the incidence of local pain and burning sensation. [CCI]

This is a Phase 1b study in healthy participants ≥50 years of age. Substudy B will investigate 2 formulations of RSVpreF + qIRV of differing volumes and osmolarities. The first combination is a bedside mix of [CCI], yielding a final injection volume of 1.0 mL [CCI]. The second combination is a bedside mix of [CCI] to yield a final injection volume of 0.5 mL. The 0.5-mL [CCI] combination would result in [CCI] with the potential to influence reactogenicity at the injection site. These combinations will be evaluated for safety, tolerability, and immunogenicity, with the goal of selecting a formulation for further study.

1.1.2.1. Objectives, Endpoints, and Estimands

Substudy B

Objectives	Endpoints	Estimands
Primary Safety	**Primary Safety**	**Primary Safety**
To evaluate the safety profile of 2 formulations of combination RSVpreF + qIRV	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	In participants receiving the study intervention, the percentage of participants reporting: • Local reactions within 7 days following vaccination • Systemic events within 7 days following vaccination • AEs throughout the study • SAEs throughout the study

Substudy B

Objectives	Endpoints	Estimands
Secondary Immunogenicity	**Secondary Immunogenicity**	**Secondary Immunogenicity**
To describe the immune responses elicited by 2 formulations of combination RSVpreF + qIRV	• RSV A and RSV B NTs • Strain-specific HAI titers for the current seasonal strains (2×A, 2×B) recommended by WHO for recombinant or cell-based influenza vaccines	In participants in compliance with the key protocol criteria (evaluable participants): • GMT for each RSV subgroup (A or B) 1 month after vaccination with each formulation • GMT of HAI titers for each of the included strains 1 month after vaccination with each formulation

1.1.2.2. Overall Design

Substudy B

Substudy B will be conducted as a Phase 1b, parallel-group, randomized, observer-blinded substudy of RSVpreF and a nucleoside-modified RNA vaccine (qIRV) against RSV and influenza administered as a combined vaccine in a 1.0-mL formulation and when administered in a 0.5-mL formulation.

Healthy adults ≥50 years of age will be randomized 1:1 to either Group 1: combination (RSVpreF + qIRV) 1.0-mL formulation; or Group 2: combination (RSVpreF + qIRV) 0.5-mL formulation. Randomization will be stratified by 6 age/sex groups (female 50-64, female 65-79, and female ≥80 years; male 50-64, male 65-79, and male ≥80 years) within the study site. Approximately 100 participants will be randomized within the 50- through 64-year-old group, and 100 participants ≥65 years of age will be randomized. Study groups, blood draws, and safety assessment timings are presented below.

Age Group N=200	Study Group Randomization 1:1 within each age cohort	Subjects per Group	Sentinel Cohort Visit B101 (Vaccination, Day 1)	Expanded Enrollment Visit B101 (Vaccination, Day 1)	Visit B102 (Follow-up, Day 28 – Day 35)
50–64 years n=100	Group 1 RSVpreF + qIRV 1.0-mL formulation*	10	RSVpreF + qIRV 1.0 mL		blood draw
		40		RSVpreF + qIRV 1.0 mL	
	Group 2 RSVpreF + qIRV 0.5-mL formulation**	10	RSVpreF + qIRV 0.5 mL		blood draw
		40		RSVpreF + qIRV 0.5 mL	
≥65 years n=100	Group 1 RSVpreF + qIRV 1.0-mL formulation*	50		RSVpreF + qIRV 1.0 mL	blood draw
	Group 2 RSVpreF + qIRV 0.5-mL formulation**	50		RSVpreF + qIRV 0.5 mL	blood draw
Safety Assessments					
Local reactions and systemic events			Days 1 through 7	Days 1 through 7	
AEs and AESIs			Consent through study completion		48 hours
SAEs			Consent through study completion		
*Group 1: 1.0-mL formulation: **Group 2: 0.5-mL formulation			CCI [redacted]		

1.1.2.3. Number of Participants

Approximately 200 healthy participants (n=100 per group) will be enrolled in Substudy B. Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process.

1.1.2.4. Study Population

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into Substudy B:

Age and Sex:

1. Participants ≥50 years of age at study enrollment.

Refer to Section 10.4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

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

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

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.11.

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

5. Receipt of licensed influenza vaccination for the 2022-2023 northern hemisphere season or 2022 southern hemisphere season >180 days before study intervention administration.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

Medical Conditions

1. A confirmed diagnosis of RSV infection or influenza ≤120 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. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate IM injection.

4. Serious chronic disorder, including metastatic malignancy, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excludes the participant from participating in the study.

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

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

Prior/Concomitant Therapy

7. Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before study intervention administration, or planned receipt throughout the study.

Note: Systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent (eg, for cancer or an autoimmune disease) or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) 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. Receipt of any RSV vaccine at any time prior to enrollment, or planned receipt throughout the study.

10. Receipt of any influenza vaccine ≤180 days before study enrollment, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience

11. Participation in other studies involving an investigational RSV vaccine or mRNA influenza vaccine at any time prior to enrollment, and thereafter until study completion, regardless of vaccine assignment.

12. Participation in any other interventional studies within 28 days before study enrollment through study completion. 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.

1.1.2.5. Study Arms and Duration

For individual participants, the duration of Substudy B is about 1 month. Based on an estimated 1-month enrollment period, the duration of Substudy B will be approximately 2 months.

Study Interventions for Substudy B

GROUP 1	Vaccine Details		
COMBINATION 1.0 mL (RSVpreF + qIRV)	Vaccine Component	RSVpreF	qIRV
		2 Stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B	Encoding HA of 4 strains as recommended for the influenza season (2 A strains and 2 B strains)
	Dose Formulation	RSV vaccine 120 µg/vial powder for solution for injection	Quadrivalent influenza suspension for injection, CCI mg/mL (qIRV)
	Product for Reconstitution	Sterile water as diluent for injection (0.65 mL/syringe)	N/A
	Unit Dose Strength(s)	120 µg	CCI µg
	Route of Administration	After combining both vaccines, a single 1-mL IM injection is given into the deltoid muscle of the nondominant arm (preferred).	
	Use	Experimental	
	IMP or NIMP/AxMP	IMP	
	Sourcing	Provided centrally by Pfizer	

GROUP 1	Vaccine Details	
	Packaging and Labeling	**RSVpreF** is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. For the 1.0-mL formulation, the white cake is CCI **qIRV** is supplied as CCI Study intervention(s) will be labeled as per country requirements.

GROUP 2	Vaccine Details		
COMBINATION 0.5 mL (RSVpreF + qIRV)	Vaccine Component	RSVpreF	qIRV
		2 Stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B	Encoding HA of 4 strains as recommended for the influenza season (2 A strains and 2 B strains)
	Dose Formulation	RSV vaccine 120 µg/vial powder for solution for injection	Quadrivalent influenza suspension for injection, CCI mg/mL (qIRV)
	Product for Reconstitution	qIRV suspension	N/A
	Unit Dose Strength(s)	120 µg	CCI µg
	Route of Administration	After combining qIRV suspension with the RSVpreF cake, a single 0.5-mL IM injection is given into the deltoid muscle of the nondominant arm (preferred).	
	Use	Experimental	
	IMP or NIMP/AxMP	IMP	
	Sourcing	Provided centrally by Pfizer	
	Packaging and Labeling	**RSVpreF** is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. For the 0.5-mL formulation, the white cake is to be CCI **qIRV** is supplied as CCI Study intervention(s) will be labeled as per country requirements.	

1.2. Ethical Considerations

The available safety, immunogenicity, and effectiveness data from ongoing clinical trials for RSVpreF, as well as data from nonclinical and clinical trials with qIRV, support a favorable benefit/risk profile and support clinical development of a vaccine combining these components. Considering the measures to minimize risk to study participants, the potential risks identified in association with the study intervention are justified by the anticipated benefits that may be afforded to healthy participants.

As qIRV has the same modRNA and LNP platform as the COVID-19 vaccine BNT162b2, its safety profile is expected to be similar to that of BNT162b2. Based on the experience with BNT162b2 and RSVpreF, the potential risks for the RSVpreF + qIRV combination vaccine include the following:

- Local reactions, such as injection site redness, injection site swelling, injection site pain, and systemic events, such as fever, fatigue, headache, chills, vomiting, nausea, diarrhea, muscle pain, and joint pain.
- Myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines (rate for myocarditis: 2.13 per 100,000 persons up to 42 days after at least 1 dose of vaccine).
- Anaphylaxis has been reported in people after vaccination with BNT162b2, at a rate of 11.1 per million doses administered.

The study procedure–related risks include:

- Participants will be required to attend healthcare facilities during seasons of heightened respiratory virus transmission.
- Venipuncture will be performed during the study.

1.3. Schema

1.3.1. Substudy A - Combination RSVpreF + qIRV vs Sequential Administration

Healthy adults ≥60 years of age (125 per group, randomized 1:1)	**Visit A101 (Day 1)**	**Visit A102 (Month 1)** 28-35 days after Vaccination 1	**Visit A103 (Month 2)** 28-35 days after Vaccination 2
	Vaccination 1	**Vaccination 2**	**Follow-up**
Group 1: Combination RSVpreF + qIRV / placebo	Combination (RSVpreF + qIRV) 	Placebo 	Blood draw 
Group 2: Sequential administration qIRV / RSVpreF	qIRV 	RSVpreF 	Blood draw 

1.3.2. Substudy B – Combination RSVpreF + qIRV 1.0-mL Formulation vs Combination RSVpreF + qIRV 0.5-mL Formulation

Substudy B Design

Age Group N=200	Study Group Randomization 1:1 within each age cohort	Participants	Sentinel Cohort Visit B101 (Vaccination, Day 1)	Expanded Enrollment Visit B101 (Vaccination, Day 1)	Visit B102 (Follow-up, Day 28 – Day 35)
50-64 years n=100	Group 1 RSVpreF + qIRV 1.0-mL formulation*	10	RSVpreF + qIRV 1.0 mL		blood draw
		40		RSVpreF + qIRV 1.0 mL	
	Group 2 RSVpreF + qIRV 0.5-mL formulation**	10	RSVpreF + qIRV 0.5 mL		blood draw
		40		RSVpreF + qIRV 0.5 mL	
≥65 years n=100	Group 1 RSVpreF + qIRV 1.0-mL formulation*	50		RSVpreF + qIRV 1.0 mL	blood draw
	Group 2 RSVpreF + qIRV 0.5-mL formulation**	50		RSVpreF + qIRV 0.5 mL	blood draw

* Group 1: 1.0-mL formulation: injection.
** Group 2: 0.5-mL formulation

CCI [redacted]

1.4. 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 10.9.3 for the Substudy A SoA.

See Section 10.10.3 for the Substudy B SoA.

2. INTRODUCTION

2.1. Study Rationale

The cocirculation of RSV and influenza significantly impacts the older adult population, where there is a higher incidence of respiratory infections and increased morbidity and mortality during the winter months.[1,2] In the early 2022-2023 US winter, the incidences of influenza and RSV-related disease were increasing.[3] As vaccines against influenza and COVID-19 can be administered at a single healthcare visit as individual vaccinations, requiring multiple injections,[4] should a licensed RSV vaccine become available, the coadministration of these vaccines would likely occur at the same time of year. The Pfizer RSV vaccine, RSVpreF, was recently found to be efficacious against RSV-associated LRTI in older adults.[5] Concurrent administration of vaccines against these respiratory viral infections reduces the need for multiple healthcare or pharmacy visits and may improve vaccine uptake. A combination vaccine with RSVpreF and qIRV would require 1 injection at a healthcare provider visit. A study of combined vaccination is required to investigate potential immunological interference in addition to safety and tolerability. Pfizer is currently investigating the efficacy of a quadrivalent modified RNA (modRNA) influenza vaccine candidate (qIRV). This study series will investigate the administration of respiratory combination vaccine candidates to assess the safety, tolerability, and potential for immunological interference. This evaluation will initially be conducted in Substudy A with RSVpreF and qIRV 1.0 mL as a Phase 1b substudy in healthy participants ≥60 years of age.

Substudy B will investigate 2 formulations of RSVpreF + qIRV of differing volume and osmolality. The first combination is a bedside mix of CCI [redacted], yielding a final injection volume of 1.0 mL. The second combination is a bedside mix of CCI [redacted] to yield a final injection volume of 0.5 mL. The 0.5-mL CCI [redacted] combination would result in CCI [redacted] These combinations will be evaluated for safety, tolerability, and immunogenicity, with the goal of selecting a formulation for further study. To better assess any relationship between age/sex and the tolerability of the study intervention,[6,7] the study population will include older adults 50 years of age and above who will be randomized by age/sex strata.

CCI [redacted]

2.2. Background

2.2.1. RSV

RSV is a major cause of respiratory infection in all ages, which can result in severe illness in both infants and older adults. There are 2 antigenic variants of RSV: subgroups A (RSV A) and B (RSV B), which cocirculate.[8] Like influenza, RSV infection follows a seasonal pattern, causing yearly wintertime epidemics in temperate climates, usually between late autumn and early spring. In tropical climates, the outbreaks are generally associated with rainy seasons but are more unpredictable and frequently continuous.[9] Because of the COVID-19 pandemic, which spread worldwide in 2020-2021, the seasonality of several pathogens, including RSV, has been disrupted and the shift of peak incidence has been observed in a majority of geographies. RSV now cocirculates with influenza and SARS-CoV-2 and increases the incidence of respiratory infection–related disease.[10]

Adults ≥60 years of age are at increased risk of RSV infection, which can trigger exacerbations of underlying comorbid conditions such as COPD and CHF. RSV infection has been associated with up to 22% of acute COPD exacerbations in prospective cohort studies and 11% of wintertime hospitalizations for COPD exacerbations.[11] Current epidemiology shows that RSV is responsible for approximately 177,000 hospitalizations and 14,000 deaths annually in US adults 65 years of age and older.[12] Morbidity is significant among adults hospitalized with RSV disease, with 18% requiring intensive care, 31% needing home health services at discharge, and 26% dying within 1 year of hospitalization.[13] In the US, RSV disease incidence rates in older adults are approximately half those of influenza, with variation year to year.[14] Incidence rates and risk for severe complications from RSV infection are higher among immunocompromised adults and those with chronic conditions (eg, cardiopulmonary or renal disease, hematological malignancies, receipt of chemotherapy, or HIV infection).[15,16] However, the burden of adult RSV disease could be underestimated since testing for RSV is less common in older adults than in children. RSV disease in adults is also difficult to diagnose based on clinical signs and symptoms alone, and, prior to the broader use of more sensitive detection methods, laboratory confirmation of RSV in adults was challenging because of low levels of virus shedding.[9]

RSV disease management in adults is limited to supportive measures, such as hydration and oxygenation. Aerosolized ribavirin has limited evidence of effectiveness and is predominantly restricted to severely immunocompromised hospitalized patients because of inconvenient administration, teratogenicity, anemia concerns, and high cost. Prevention of RSV disease via active immunization has the potential to make a significant impact in this population, therefore making vaccine development a high priority.[16,17]

2.2.1.1. RSVpreF Vaccination

RSVpreF is a bivalent RSV prefusion F subunit vaccine developed by Pfizer. The RSV F glycoprotein facilitates fusion of the virion and host cell membrane through a dramatic transition from an unstable but highly immunogenic prefusion conformation to the more stable postfusion state. Preclinical studies show that prefusion F elicits much higher neutralizing antibody titers than postfusion F and that the most potent neutralizing antibodies from postinfection human sera target the prefusion form. RSVpreF is composed of engineered, stabilized, trimeric, prefusion F glycoproteins matching the 2 subgroups (A and B) to help ensure the broadest coverage against RSV illness.

RSVpreF is being developed for 2 indications:

- **Older Adult:** Prevention of LRTI-RSV in adults 60 years of age and older via active immunization.
- **Maternal:** Prevention of LRTI-RSV in infants by active immunization of pregnant women.

As of December 2022, RSVpreF has been studied in 6 completed trials in healthy adults and pregnant women and 2 ongoing Phase 3 clinical trials in older adults and infants born to vaccinated pregnant women. RSVpreF was shown to be well tolerated, with an acceptable safety profile, and highly efficacious in older adults and infants of women vaccinated during pregnancy.

2.2.2. Influenza

Influenza is a major cause of morbidity and mortality worldwide, occurring in annual seasonal epidemics and occasionally in global pandemics.[18] Symptomatic influenza infection causes a febrile illness with respiratory and systemic symptoms,[19] although it may often be asymptomatic.[20] 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,[21] while the annual global number of deaths is estimated to range from almost 300,000 to over 600,000.[22]

Influenza viruses are part of the *Orthomyxoviridae* family and are divided into 3 genera or types (A, B, and C) based upon antigenic differences in the nucleoprotein and matrix protein. Influenza A viruses are further classified into subtypes based upon the membrane glycoproteins, HA and NA.[23] The RNA genome is segmented, which allows genetic reassortment among viruses of the same type.[23] This genetic instability can result in the phenomenon known as antigenic shift, involving a major change in 1 or both of the HAs and NAs, which, if efficiently transmissible, can result in a pandemic. More common are multiple point mutations in the genome, leading to more minor changes in the HA and NA, known as antigenic drift.[21] This genetic instability is what necessitates vaccines that are tailored annually.[21]

2.2.2.1. Influenza Vaccination

The first influenza vaccines were licensed in the 1940s,[24] and now a number of different types of vaccine exist: inactivated, recombinant, and LAIV.[25] The viruses that form the basis for inactivated vaccines are replicated in either embryonated hens' eggs or mammalian cell lines,[26] and some are combined with an adjuvant, such as MF59, to improve the immune response, particularly important in older individuals.[25]

Multivalent vaccines are produced for routine seasonal immunization, targeting 3 or 4 influenza viruses.[25] Trivalent vaccines target 2 A subtypes and 1 B virus, although these have been replaced by quadrivalent vaccines that target an additional B virus (because of the emergence of 2 antigenically distinct lineages).[27] Standard inactivated vaccines generally contain 15 µg of each HA for adult IM injection, although the high-dose inactivated vaccine contains 60 µg of each HA.[28]

Annual seasonal influenza vaccination is recommended in a number of countries around the world to prevent influenza in children and adults. Older adults, particularly those with medical comorbidities, are at increased risk of influenza morbidity and mortality and are recommended to receive high-dose or adjuvanted influenza vaccine formulations.[29] 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.[28] This means that the schedule for vaccine production, release, and administration is highly compressed.

In the last several years, the use of mRNA as the basis for potential vaccine candidates has shown increasing promise.[30] Various approaches to optimize the response to mRNA vaccines have been used. This includes modRNA in which some nucleosides are replaced by naturally occurring modified nucleosides, such as pseudouridine, which decreases innate immune activation and increases translation.[30] 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)[31] and mRNA-1273 (Moderna),[32] with both vaccines demonstrating high effectiveness with no significant safety concerns during Phase 3 development.[31,33] Since its first marketing authorization in December 2020, BNT162b2 has been administered to hundreds of millions of individuals worldwide. Postauthorization safety surveillance in the US has confirmed the safety profile observed in clinical trials and has also identified adverse reactions of anaphylaxis (estimated at 11.1 per million doses administered) and an increased risk of myocarditis and pericarditis (rate for myocarditis: 2.13 per 100,000 persons up to 42 days after at least 1 dose of vaccine), primarily in adolescents and young adult males.[34,35,36,37]

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

A Phase 3, randomized, observer-blinded study to evaluate the safety, tolerability, and immunogenicity of quadrivalent modRNA-based influenza vaccine is ongoing; at the time of protocol authorship, approximately 25,000 participants 18 years of age and older have been enrolled in this study and randomized 1:1 to receive either qIRV or comparator. modRNA-based influenza vaccine encodes HA of 4 strains (2 A strains and 2 B strains) recommended for the 2022-2023 northern hemisphere influenza season.

2.2.3. Clinical Overview

2.2.3.1. RSVpreF

The older adult program includes 2 Phase 1/2 studies, 3 Phase 3 studies, and a Phase 2a human challenge study.

In the Phase 1/2 study C3671001, 1233 healthy adults 18 through 49 and 50 through 85 years of age received 3 dose levels of RSVpreF (60 µg, 120 µg, and 240 µg), with or without $Al(OH)_3$, or placebo, administered with or without concomitant influenza vaccine. The results have shown that the vaccine was well tolerated and immunogenic in both age groups. RSVpreF elicited robust neutralizing responses against RSV A and RSV B 1 month after vaccination for both age groups across all vaccine dose levels and formulations; these responses remained high through the 12 months after vaccination. In 616 vaccinated participants in the 50- through 85-year age group, RSV 50% NT GMFRs were high across all study groups, ranging from 9 to 13 from before vaccination through 1 month after vaccination and from 3 to 4 from before vaccination through 12 months for RSV A and RSV B. RSVpreF was safe and well tolerated when administered alone or with SIIV, with no major differences observed across all dose levels and formulations. Most reported local reactions or systemic events were mild or moderate in severity.

The proportions of participants reporting AEs were generally similar across RSVpreF groups, and no SAEs were considered related to the investigational vaccine.

Phase 1/2 study C3671002, in 313 older adults 65 through 85 years of age, studied the 3 dose levels of RSVpreF with $Al(OH)_3$, or $CpG/Al(OH)_3$ (60 µg, 120 µg, and 240 µg), given as a single dose or on a schedule of 2 doses administered 2 months apart. All RSVpreF doses and formulations elicited high RSV A– and RSV B–neutralizing antibody GMTs 1 month after vaccination (GMFRs ranging from 4.8 to 11.6 and 4.5 to 14.1, respectively). CpG-containing formulations did not further increase neutralizing GMTs compared to RSVpreF with or without $Al(OH)_3$. GMTs in all groups declined but remained higher than baseline (before vaccination) and placebo (SIIV only) at 12 months after vaccination (GMFRs ranging from 2.1 to 3.5 and 2.2 to 4.3, respectively). No increase in GMTs was observed 1 month after Vaccination 2 (GMFR of 0.9). All doses and formulations were safe and well tolerated.

Study C3671014 is a completed Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind lot-consistency study in a population of up to 1000 healthy adults 18 to ≤49 years of age. The study examined the immune response and the safety and tolerability profiles across 3 manufactured lots of RSVpreF when administered as a single 120-µg dose to healthy adults. The primary analyses showed that the ratios of neutralizing

GMTs for each of the 3 manufactured RSVpreF lots 1 month after vaccination are equivalent, and that the 120-µg dose of RSVpreF is well tolerated and has an acceptable safety profile.

A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Immunogenicity and Efficacy of a Respiratory Syncytial Virus Vaccine (RSVpreF) in a Virus Challenge Model in Healthy Adults (NCT04785612) was conducted by hVIVO in 70 healthy participants 18 to 50 years of age. Participants received a single dose of either 120 µg RSVpreF or placebo and 4 weeks later underwent intranasal challenge with RSV A Memphis 37b virus. The immunogenicity and efficacy of RSVpreF vaccination on virus replication, clinical symptoms, and incidence of symptomatic RSV infection following the intranasal challenge were evaluated. The primary analysis of the human challenge study showed that a 120-µg dose of RSVpreF was well tolerated and has an acceptable safety profile. The study demonstrated 100% efficacy of RSVpreF against RT-PCR–confirmed symptomatic infection.

C3671013 is an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the safety, immunogenicity, and efficacy of Pfizer's RSVpreF in prevention of RSV-associated LRTI in adults 60 years of age and older. Both healthy adults and adults with stable chronic cardiopulmonary conditions are included. Approximately 10% of participants with stable chronic cardiopulmonary conditions such as COPD, asthma, or CHF are being enrolled. The study enrolled over 37,000 participants, randomized to receive RSVpreF or placebo in a 1:1 ratio. This is an event-driven study with a target of 59 first episodes of evaluable RSV-associated LRTI cases. Interim analysis results in August 2022 showed protection against LRTI-RSV defined by 2 or more symptoms demonstrated vaccine efficacy: 66.7%. Vaccine efficacy of 85.7% was observed in participants with a more severe disease primary endpoint of LRTI-RSV defined by analysis of 3 or more RSV-associated symptoms. The vaccine was well tolerated, with no safety concerns.

C3671006 is a Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study. 1403 healthy adults ≥65 years of age were randomized 1:1 to either a coadministration group or a sequential-administration group. The intention of this study was to demonstrate that the immune responses generated when a 120-µg RSVpreF dose was coadministered with SIIV were noninferior to the immune responses when these products were administered 4 weeks apart. The safety and tolerability of RSVpreF were also examined. Results demonstrated noninferiority of the RSVpreF and SIIV immune responses when RSVpreF was coadministered with SIIV. The results of this study support the acceptability of coadministration of RSVpreF and SIIV in an older adult population.

RSVpreF is also being studied in the maternal program, which includes Phase 2b and Phase 3 studies in pregnant women and a Phase 2b study in nonpregnant women. Details of each of these studies are provided in the RSVpreF IB.

2.2.3.2. qIRV

A Phase 1/2 study (C4781001) to describe the safety, tolerability, and immunogenicity of a modRNA vaccine against influenza in healthy individuals was initiated in September 2021 in participants 65 through 85 years of age. This study is being conducted across 2 substudies – Substudy A and Substudy B. Substudy A is being conducted to describe the safety and immunogenicity of mIRV encoding subgroup A or B strains at 4 dose levels, bIRV encoding both A and B strains in 4 dose-level combinations, and qIRV encoding 2 A strains and 2 B strains at a dose level of [CCI] µg per strain. Substudy B will describe the safety, tolerability, and immunogenicity of modRNA influenza vaccines when administered in differing vaccination schedules.

Preliminary results from Study C4781001 from participants 65 through 85 years of age indicate that qIRV at a [CCI]- or [CCI]-µg dose level is well tolerated, with mainly mild to moderate local reactions and systemic events consistent with rates observed with BNT162b2 and supported the initiation of a global Phase 3 study, C4781004. Immunogenicity data from C4781001 available to date indicated that:

- For A/Wisconsin and A/Cambodia, the proportion of participants achieving seroconversion 4 weeks following either 1 or 2 doses of qIRV, at a total dose level of [CCI] µg per dose, was higher than the proportion of participants achieving seroconversion following either 1 or 2 doses of QIV. Additionally, at 4 weeks following QIV administered with bIRV encoding 2 A strains at a total dose of [CCI] or [CCI] µg ([CCI] or [CCI] µg per strain), either concurrently or 21 days apart, the proportion of participants achieving seroconversion also appeared to be higher than the proportion of participants achieving seroconversion following either 1 or 2 doses of QIV.

- For B/Phuket and B/Washington, the proportion of participants achieving seroconversion 4 weeks following study intervention in all groups, including 1- and 2-dose QIV recipients, was lower compared to the proportion of participants achieving seroconversion against A/Wisconsin and A/Cambodia. For B/Phuket and B/Washington, the proportion of participants achieving seroconversion 4 weeks following either 1 or 2 doses of qIRV, at a total dose level of [CCI] µg per dose, or following QIV administered with bIRV encoding 2 A strains at a total dose level of either [CCI] or [CCI] µg ([CCI] or [CCI] µg per strain), either concurrently or 21 days apart, appeared to be generally less than or equal to the proportion of participants achieving seroconversion following either 1 or 2 doses of QIV.

The qIRV vaccine has been administered to approximately 8500 participants ≥65 years of age in the C4781004 study. Ongoing safety review from this blinded study has been overseen by an independent data review monitoring committee and continued study dosing has been endorsed as of May 2023.

The latest safety and immunogenicity results can be found in the IB for qIRV. Based on the safety and immunogenicity data from Study C4781001, 1 dose of qIRV encoding 2 A strains and 2 B strains has been selected for study in Phase 3, [CCI] µg for participants 18 through 64 years of age and [CCI] µg for participants ≥65 years of age.

2.3. Benefit/Risk Assessment

RSV and influenza are typically seasonal diseases, with peaks during winter in temperate climates.[8] Therefore, it is a reasonable possibility that RSVpreF may be given at the same time as seasonal influenza vaccine.

Given that annual vaccine programs against both influenza and RSV may be conducted in the future at a similar time of year, developing a combined vaccine targeting both viruses is likely to generate overall higher vaccination rates for both viruses and allow for more convenient scheduling than if these vaccinations were to be administered separately.

The available safety, immunogenicity, and effectiveness data from ongoing clinical trials for RSVpreF, as well as data from nonclinical and clinical trials with qIRV, support a favorable benefit/risk profile and support clinical development of a vaccine combining these components. As qIRV has the same modRNA and LNP platform as the COVID-19 vaccine BNT162b2, its safety profile is expected to be similar to that of BNT162b2.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of RSVpreF and qIRV may be found in the RSVpreF and qIRV IBs, which are the SRSDs for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): Combination RSVpreF + qIRV		
For **RSVpreF**: Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) following vaccination. For **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.	The most common reactions reported with vaccination in general[38] are also reported for **RSVpreF**. These are common adverse reactions seen with other vaccines as well as RSVpreF. The most common events reported in Studies C3671008 and C3671013 were mild to moderate pain at the injection site, headache, and muscle pain. For **qIRV**: 1-Week follow-up reactogenicity data of 194 participants who received mIRV, bIRV, or qIRV in C4781001 Substudy A and 120 participants from C4781001 Substudy B showed most events to be mild to moderate in severity, with the most common events being pain at the injection site, fatigue, and headache. qIRV has been administered to approximately 8500 participants ≥65 years of age in the C4781004 study. Ongoing safety review from this blinded study has been overseen by an independent data review monitoring committee and continued study dosing has been endorsed as of May 2023.	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. Collection of AEs and SAEs will be conducted from signing of the ICD through 4 weeks after the participant's last study vaccination.
The safety profile of the novel vaccine is close to being, but not yet fully, characterized.	Although qIRVs are novel vaccines, they are based on the same platform (modRNA) as the COVID-19 vaccine BNT162b2, which has been shown to have a positive benefit/risk profile.	Assessments of AEs and SAEs will be collected and reviewed throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Although qIRVs are novel vaccines, they are based on the same platform (modRNA) as the COVID-19 vaccine BNT162b2. Cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.	Anaphylaxis has been reported in people after vaccination with BNT162b2, at a rate of 11.1 per million doses administered.[35] Myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines (rate for myocarditis: 2.13 per 100,000 persons up to 42 days after at least 1 dose of vaccine).[36] Typically, the cases have occurred more often in younger men and after the second dose of the vaccine, within several days after vaccination.[39] 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. The mechanism by which mRNA COVID-19 vaccines could trigger cases of myocarditis and pericarditis has not been elucidated. If it relates to the modRNA or LNP formulation, rather than the encoded antigen(s), it is plausible that the same risk, risk factors, and prognosis may exist for influenza modRNA vaccines.	For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. Receipt of any mRNA-platform SARS-CoV-2 vaccine within 14 days before and 14 days after study vaccination is prohibited. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 10.9.10.6.4.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): RSVpreF		
Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) following vaccination.	The most common reactions reported with vaccination in general[38] are also reported for RSVpreF. These are common adverse reactions seen with other vaccines as well as RSVpreF. The most common events reported in Studies C3671008 and C3671013 were mild to moderate pain at the injection site, headache, and muscle pain.	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. Collection of AEs and SAEs will be conducted from signing of the ICD through study completion.
The safety profile of the novel vaccine is close to being, but not yet fully, characterized.	Data available from completed and ongoing RSVpreF studies showed a low incidence of severe or serious events and no clinically concerning safety observations. The vaccine appears to be safe and well tolerated across the safety population and within demographic subgroups based on age, sex, and race/ethnicity.	Collection of AEs and SAEs will be conducted throughout the study. All participants will be observed for at least 30 minutes after vaccination.
Study Intervention(s): qIRV		
Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination. No safety data are available regarding the use of qIRV in participants ≥65 years of age.	1-Week follow-up reactogenicity data of 194 participants who received mIRV, bIRV, or qIRV in C4781001 Substudy A and 120 participants from C4781001 Substudy B showed most events to be mild to moderate in severity, with the most common events being pain at the injection site, fatigue, and headache.	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol. Collection of AEs and SAEs will be conducted from signing of the ICD through study completion. For anaphylaxis, there is an on-site 30-minute observation period after vaccination.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Anaphylaxis has been reported in people after vaccination with BNT162b2, at a rate of 11.1 per million doses administered.[35]	
The safety profile of the novel vaccine is close to being, but not yet fully, characterized.	Although qIRVs are novel vaccines, they are based on the same platform (modRNA) as the COVID-19 vaccine BNT162b2, which has been shown to have a positive benefit/risk profile.	Assessments of AEs and SAEs will be collected and reviewed throughout the study.
Although qIRVs are novel vaccines, they are based on the same platform (modRNA) as the COVID-19 vaccine BNT162b2. Cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.	Anaphylaxis has been reported in people after vaccination with BNT162b2, at a rate of 11.1 per million doses administered.[35] Myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines (rate for myocarditis: 2.13 per 100,000 persons up to 42 days after at least 1 dose of vaccine).[36] Typically, the cases have occurred more often in younger men and after the second dose of the vaccine, within several days after vaccination.[39] 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. The mechanism by which mRNA COVID-19 vaccines could trigger cases of myocarditis and pericarditis has not been elucidated. If it relates to the modRNA or LNP formulation, rather than the encoded antigen(s), it is plausible that the same risk, risk factors, and prognosis may exist for influenza modRNA vaccines.	Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. Receipt of any mRNA-platform SARS-CoV-2 vaccine within 14 days before and 14 days after study vaccination is prohibited. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 10.9.10.6.4.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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.
Participants will be required to attend healthcare facilities during seasons of heightened respiratory virus transmission.	There is the potential for increased exposure to SARS-CoV-2, influenza, and RSV.	Pfizer will work with sites to ensure appropriate transmissible respiratory illness prevention strategies. Cases of COVID-19, influenza, and RSV will be reported as AEs or SAEs.

2.3.2. Benefit Assessment

Benefits to individual participants enrolled in Substudy A are given in Section 10.9.4.3.

Benefits to individual participants enrolled in Substudy B are given in Section 10.10.4.3.

2.3.3. For Substudy A and Substudy B Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants as stated in Section 2.3.1, the potential risks identified in association with RSVpreF and qIRV are justified by the anticipated benefits that may be afforded to healthy participants in Substudy A (Section 10.9.4.3) and Substudy B (Section 10.10.4.3).

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

See Section 10.9.5 for the Substudy A objectives, endpoints, and estimands.

See Section 10.10.5 for the Substudy B objectives, endpoints, and estimands.

4. STUDY DESIGN

4.1. Overall Design

See Section 10.9.6.1 for the Substudy A design.

See Section 10.10.6.1 for the Substudy B design.

4.2. Scientific Rationale for Study Design

See Section 2.1 for the rationale for the design of Substudy A and Substudy B.

4.2.1. Diversity of Study Population

Where supported by geographical location, the diversity strategy for this study will include the following:

- Selecting sites that have access to diverse participants within their locale.
- Educating sites about the importance of increasing diversity on clinical trials and Pfizer commitment.
- Investigator site recruitment plans that are cocreated with and include diverse recruitment tools and information to support enrollment. Real-world data are used to target outreach and potential referring physicians.
- Continual monitoring of diverse enrollment to identify additional opportunities to include diverse populations.

4.2.2. Choice of Contraception/Barrier Requirements

There is no suspicion of human teratogenicity based on the available reproductive toxicity data; however, human reproductive safety data are limited, and a Phase 3 study of RSVpreF in more than 7000 pregnant women is ongoing. Human reproductive safety data are not available for the mRNA influenza vaccines used in this study, 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 (Section 10.4.4).

4.3. Justification for Dose

4.3.1. RSVpreF

The dose and formulation for this study is 120 µg RSVpreF without any adjuvants.

The FIH study in adults 18 through 85 years of age evaluated the safety, tolerability, and immunogenicity of 3 escalating RSVpreF dose levels of 60 µg, 120 µg, and 240 µg, with or without $Al(OH)_3$, when administered alone or concomitantly with SIIV (Study C3671001).

A study in older adults 65 through 85 years of age evaluated the safety, tolerability, and immunogenicity of 60-µg, 120-µg, and 240-µg RSVpreF doses formulated with $Al(OH)_3$ or a CpG/$Al(OH)_3$ adjuvant, or 240 µg RSVpreF with RSV antigens alone, when administered concomitantly with SIIV (Study C3671002).

A Phase 3 study in adults 65 years of age and older evaluated the safety, tolerability, and immunogenicity of 120 µg RSVpreF when administered concomitantly with SIIV (Study C3671006).

A study in healthy adults 18 through 50 years of age evaluated the safety, immunogenicity, and efficacy of 120 µg RSVpreF in a virus challenge model (NCT04785612).

4.3.2. qIRV

Based on the safety and immunogenicity data from Phase 1 of the C4781001 study, 1 dose of qIRV encoding 2 A strains and 2 B strains, CCI µg CCI µg per strain), was selected for participants 18 through 64 years of age in the Phase 2 C4781001 substudy and for participants ≥65 years of age in the Phase 3 study (C4781004). The same dose will be administered in this protocol. The latest safety and immunogenicity results can be found in the IB for qIRV.

4.4. End of Study Definition

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

A participant is considered to have completed the study when she/he has completed all study visits.

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.

5.1. Inclusion Criteria

See Section 10.9.7.1 for the Substudy A inclusion criteria.

See Section 10.10.7.1 for the Substudy B inclusion criteria.

5.2. Exclusion Criteria

See Section 10.9.7.2 for the Substudy A exclusion criteria.

See Section 10.10.7.2 for the Substudy B exclusion criteria.

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 from the permitted list of contraception methods (Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

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

5.4. Screen Failures

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

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

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention (Substudy A and Substudy B)

The following conditions are temporary or self-limiting and a participant may be randomized (Visit A101) and vaccinated (Visit A101, Visit A102, and Visit B101) once the condition(s) has/have resolved.

1. Current febrile illness (oral temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study intervention administration.

2. Receipt of any inactivated or recombinant vaccine, licensed COVID-19 vaccine, or COVID-19 vaccine authorized for temporary or emergency use within 14 days, or any live vaccine within 28 days, before study intervention administration.

3. Receipt of short-term (<14 days) systemic corticosteroids (equivalent of ≥20 mg/day of prednisone). Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, ears) corticosteroids are permitted.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s)

For the purposes of this protocol, study intervention refers to the following products:

6.1.1. Combination RSVpreF + qIRV (Substudy A and Substudy B)

RSVpreF + qIRV, which is a combination of the following vaccine candidates:

- 120 µg RSVpreF containing 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B

- CCI µg qIRV, ie, encoding HA of 4 strains as recommended for the influenza season (2 A strains and 2 B strains, at a dose of CCI µg per strain)

6.1.2. RSVpreF (Substudy A)

- 120 µg RSVpreF containing 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B

6.1.3. qIRV (Substudy A)

- CCI µg qIRV, encoding HA of 4 strains as recommended for the influenza season (2 A strains and 2 B strains, at a dose of CCI µg per strain)

6.1.4. Placebo (Substudy A)

- The placebo is 0.9% normal saline for injection.

6.2. Study Intervention(s) Administered

See Section 10.9.8.1 for study interventions to be administered during Substudy A.

See Section 10.10.8.1 for study interventions to be administered during Substudy B.

6.2.1. Administration

All study interventions are to be administered as an IM injection into the deltoid muscle, preferably of the nondominant arm.

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

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

Study intervention administration details will be recorded on the CRF.

See Section 10.9.8.1 for additional administration details for Substudy A.

See Section 10.10.8.1 for additional administration details for Substudy B.

6.2.2. Medical Devices

In this study, the PFS and vial adapter required for the preparation of RSVpreF are considered medical devices. For Substudy A and Substudy B (1.0-mL formulation), RSVpreF will be provided in a kit that contains a vial of RSVpreF lyophilized powder, a PFS containing sterile water, and a vial adapter. Instructions for their use are provided in the IPM.

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

6.3. Preparation, Handling, Storage, and Accountability

- 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.

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

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

- 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.

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

- Study interventions should be stored in their original containers.

- 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.

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.

6.3.1. Preparation and Dispensing

See the IPM for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an unblinded, 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 unblinded staff member will verify the dispensing.

6.4. Assignment to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed using 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 corresponding to the assigned vaccine group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. This report will be provided to blinded or unblinded site staff as appropriate on the role/permission the user is granted and must be stored in the site's blinded or unblinded files as appropriate.

Study intervention will be dispensed at the study visits summarized in the SoA – Substudy A or Schedule of Activities – Substudy B.

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

6.5. Blinding

See Section 10.9.8.2 for Substudy A blinding arrangements.

See Section 10.10.8.2 for Substudy B blinding arrangements.

6.5.1. Blinding of Participants

Substudy A blinding arrangements for participants are detailed in Section 10.9.8.2.1.

Substudy B blinding arrangements for participants are detailed in Section 10.10.8.2.1.

6.5.2. Blinding of Site Personnel

Substudy A blinding arrangements for site personnel are detailed in Section 10.9.8.2.2.

Substudy B blinding arrangements for site personnel are detailed in Section 10.10.8.2.2.

6.5.3. Blinding of the Sponsor

Substudy A blinding arrangements for the sponsor are detailed in Section 10.9.8.2.3.

Substudy B blinding arrangements for the sponsor are detailed in Section 10.10.8.2.3.

6.5.4. Breaking the Blind

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

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

6.6. 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.

For Substudy A and Substudy B, the preparation and administration of study intervention will be done by unblinded study staff. Additional information is provided in the IPM.

6.7. Dose Modification

Dose modification is not applicable to this protocol.

6.8. 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. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.9. Treatment of Overdose

Any more than 1 dose of the same 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:

- Contact the study medical monitor within 24 hours.
- Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
- Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

6.10. Prior and Concomitant Therapy

See Section 10.9.8.7 for Substudy A prior and concomitant therapy.

See Section 10.10.8.7 for Substudy B prior and concomitant therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety and where applicable, immunogenicity. See the SoA – Substudy A or Schedule of Activities – Substudy B for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;
- Lost to follow-up;

- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Selected protocol deviations.

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 return to the clinic for a required study visit:

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the SoA.

Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA – Substudy A, 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.

8.1.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants as specified in the SoA – Substudy A or Schedule of Activities – Substudy B.

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring.

The following assessments must be performed during a telehealth visit (see the SoA – Substudy A or Schedule of Activities – Substudy B):

- Review and record any AEs and SAEs since the last contact. Refer to Section 10.3.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Study participants must be reminded to promptly notify site staff about any change in their health status.
- Obtain stop dates for previously reported AEs and SAEs.
- Obtain stop dates for any reactogenicity events reported as present on the last day of e-diary completion.
- Record the use of prohibited medications in the CRF as noted in Section 10.9.8.7.1 (Substudy A) and Section 10.10.8.7.1 (Substudy B).
- Record the use of any new nonstudy vaccines in the CRF.

8.2. Efficacy and/or Immunogenicity Assessments

8.2.1. Efficacy Assessments

Not applicable.

8.2.2. Immunogenicity Assessments

See Section 10.9.10.1 for Substudy A immunogenicity assessments.

See Section 10.10.10.1 for Substudy B immunogenicity assessments.

8.2.3. Biological Samples

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory analyst testing the samples will not know the participant's identity, study visit, or study cohort associated with the sample. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other vaccines or

vaccine-related products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that their samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained, and no testing of the participant's genetic material/DNA is performed.

8.3. Safety Assessments

Substudy A planned time points for all safety assessments are provided in the SoA – Substudy A.

Substudy B planned time points for all safety assessments are provided in the Schedule of Activities – Substudy B.

Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment and 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 each study intervention will be assessed and documented in the AE CRF.

Safety parameters also include reactogenicity e-diary reports of local reactions, systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Table 1, Table 2, and Table 3.

8.3.1. Physical Examinations and Clinical Assessments

A clinical assessment is to be performed prior to any study vaccination. (Please refer to the SoA – Substudy A and Schedule of Activities – Substudy B for the study time point[s] requiring clinical assessment.)

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

A physical examination will include vital signs (oral or tympanic temperature, pulse rate, and seated blood pressure) and evaluation of 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.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Section 10.3) must be reported according to the processes in Section 8.4.

8.3.2. Vital Signs

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Section 10.3) must be reported according to the processes in Section 10.3.3.

8.3.2.1. Blood Pressure and Pulse Rate

For Substudy A, the participant's pulse rate and seated blood pressure will be measured prior to vaccination at Visit A101.

For Substudy B, the participant's pulse rate and seated blood pressure will be measured prior to vaccination at Visit B101.

8.3.2.2. Temperature

The participant's oral or tympanic temperature will be measured prior to each vaccination and, if clinically indicated, at any unscheduled reactogenicity visits.

8.3.3. Clinical Safety Laboratory Assessments

For Substudy A, clinical safety laboratory assessments will not be collected. Measurement of troponin will be performed locally for potential myocarditis/pericarditis evaluation. Refer to Section 10.9.10.6.4.2.

For Substudy B, clinical safety laboratory assessments will not be collected. Measurement of troponin will be performed locally for potential myocarditis/pericarditis evaluation. Refer to Section 10.10.10.6.3.2.

8.3.4. Electronic Diary

Participants will be required to complete a reactogenicity e-diary after each vaccination through an application installed on a provisioned device or on the participant's own personal device. All participants will be asked to monitor and record local reactions, systemic events, and use of antipyretic medication used to treat postvaccination symptoms, for 7 days from the day of administration of each study intervention. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will always be available for review by investigators and the Pfizer clinicians 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. To avoid duplicate reporting, e-diary data are not reported in the CRF as AEs.

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

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

8.3.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[38]

8.3.4.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary.

If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the investigator will enter this information into the CRF and follow up at the next study visit to obtain stop dates for local reactions that have resolved.

Participants will be provided with a measuring device. Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 1.

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

Table 1. Local Reaction Grading Scale

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	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 can 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 contact with the participant. Grade 4 local reactions will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.3.3.

8.3.4.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, nausea, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a systemic event persists beyond the end of the reactogenicity e-diary period following vaccination, the investigator will enter this information into the CRF and follow up at the next study visit to obtain stop dates for the events that have resolved.

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 can classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fatigue (= tiredness)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache

Table 2. Systemic Event Grading Scale

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization for severe vomiting
Nausea	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe nausea
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
Chills	Does not interfere with activity	Some interference with activity	Precents 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 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 joint pain

a. Only an investigator or qualified designee can 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 contact with the participant. Grade 4 systemic events will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.3.3.

8.3.4.4. Fever Monitoring

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 7-day reactogenicity e-diary reporting periods. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary, where possible. 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 ranges shown in Table 3 during analysis.

If a fever of ≥39.0°C (≥102.1°F) is reported in the e-diary, a telephone contact with the participant should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person can 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. Grade 4 fevers will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.3.3.

Table 3. Ranges for Fever

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fever	≥38.0°C to 38.4°C (100.4-101.1°F)	>38.4°C to 38.9°C (101.2-102.0°F)	>38.9°C to 40.0°C (102.1-104.0°F)	>40.0°C (>104.0°F)

a. Only an investigator or qualified designee can classify a participant's fever as Grade 4, after clinical evaluation of the participant, documentation from another medically qualified source (eg, emergency room or hospital record), or contact with the participant. Grade 4 fevers will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.3.3.

8.3.4.5. Antipyretic Medication

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

8.3.5. Pregnancy Testing

Urine pregnancy tests must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at Visit B101, before the administration of the dose of study intervention. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will not be administered the study intervention and will be withdrawn from the study.

8.3.6. Stopping Rules

Stopping rules will be employed in Substudy A; see Section 10.9.10.5.

Stopping rules will be employed in Substudy B; see Section 10.10.10.5.

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

The definitions of an AE and an SAE can be found in Section 10.3.

The definitions of device-related safety events (ADEs and SADEs) can be found in Sections 10.8.1 and 10.8.2. Device deficiencies are covered in Section 10.8.3.

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

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

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

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

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

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

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. 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.

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

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

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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 Section 10.3.

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.

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 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 injection or skin contact.
- A male family member or healthcare provider who has been exposed to the study intervention by injection 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's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the study intervention.

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

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

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female 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 injection or skin contact.

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

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;
- Confirmed diagnosis of RSV infection;

- Confirmed diagnosis of myocarditis or pericarditis within 4 weeks after administration of the first study vaccination. See Section 10.9.10.6.4.2 (Substudy A) and Section 10.10.10.6.3.2 (Substudy B) for additional procedures for monitoring of potential myocarditis or pericarditis.

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

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

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.2.2. In order to fulfill regulatory reporting obligations worldwide, the unblinded site staff is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.8.3.

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 to 8.4.4 and Section 10.3 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.

The method of documenting medical device deficiencies is provided in Section 10.8.4.

8.4.9.2. Follow-Up of Medical Device Deficiencies

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

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

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

8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The unblinded site staff notifies the sponsor by telephone or email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

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

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

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

8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies

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

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

8.4.10. Vaccination Errors

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

Vaccination errors are recorded and reported as follows:

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

Vaccination errors include:

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

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

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

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Refer to Section 10.9.10.1 for immunogenicity assessments for Substudy A.

Refer to Section 10.10.10.1 for immunogenicity assessments for Substudy B.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypothesis

Refer to Section 10.9.11.1 for statistical hypotheses for Substudy A.

Refer to Section 10.10.11.1 for statistical hypotheses for Substudy B.

9.2. Analysis Sets

Refer to Section 10.9.11.2 for analysis sets for Substudy A.

Refer to Section 10.10.11.2 for analysis sets for Substudy B.

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 and secondary endpoints.

Statistical analyses for Substudy A are detailed in Section 10.9.11.3.

Statistical analyses for Substudy B are detailed in Section 0.

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. Missing AE dates will be imputed according to Pfizer safety rules.

Completely missing e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For partially complete e-diary data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on missing days based on the e-diary data source. For participants with e-diary data transmitted, related reactogenicity data reported within 7 days after vaccination may be included in the analysis.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population(s). An additional analysis may be performed based on the mITT population. Participants will be summarized according to the group to which they were randomized.

9.3.1.1. Analyses for Binary Data

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

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[40]

The 95% CI for the difference in the proportions will be computed using the Miettinen and Nurminen method.[40] The 95% CI will be presented in terms of percentage.

9.3.1.2. Analyses for Continuous Data

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

9.3.1.2.1. Geometric Means

Continuous immunogenicity endpoints will be logarithmically transformed for analysis. Geometric means and associated 2-sided 95% CIs will be derived by calculating group means and CIs on the natural log scale based on the t distribution, and then exponentiating the results.

9.3.1.2.2. Geometric Mean Fold Rises

GMFRs will be calculated as the group mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. GMFRs are limited to participants with nonmissing values at both time points. 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. Geometric Mean Ratios

The GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 vaccine groups and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using the Student t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

9.3.1.2.4. Reverse Cumulative Distribution Curves

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

9.4. Interim Analyses

Not applicable.

9.5. Sample Size Determination

Refer to Section 10.9.11.5 for sample size determination for Substudy A.

Refer to Section 10.10.11.5 for sample size determination for Substudy B.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an IRC. The IRC is independent of the study team and includes only internal members. The IRC charter describes the role of the IRC in more detail.
The IRC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data to regulatory authorities and investigators, as appropriate.

The responsibilities of the IRC will include at a minimum:

- Review of safety data in the case of a stopping rule being met.

This study will not use an EDMC.

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.

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 form and are password protected 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.

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

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

10.1.8. Source Documents

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

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

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

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

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

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

10.1.9. Study and Site Start and Closure

The study start date is the date 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.

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

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

10.1.10. Publication Policy

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

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

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

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

10.1.11. Sponsor's Medically Qualified Individual

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

Routine clinical laboratory tests are not applicable to Substudy A.

Routine clinical laboratory tests are not applicable to Substudy B.

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 Meeting the AE Definition

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

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

10.3.2. 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.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. 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.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the Vaccine SAE Reporting Form

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

10.4.1.1. Substudy A and Substudy B

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.
- Be vasectomized and the absence of sperm has been confirmed.

  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.

10.4.2. Female Participant Reproductive Inclusion Criteria

10.4.2.1. Substudy A

A female participant is eligible to participate if she is not a WOCBP (see definitions below in Section 10.4.3).

10.4.2.2. Substudy B

The criteria below are part of inclusion criterion 1 (Age and Sex; Section 10.10.7.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4.2 for a complete list of contraceptive methods permitted in the study.

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

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

  OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

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

10.4.4. 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.

10.4.4.1. Substudy A

The following contraceptive methods are appropriate for Substudy A:

- As all female participants in Substudy A are at least 60 years of age, contraceptive use is not required for females.
- Refer to Section 10.4.1 for male participants.

10.4.4.2. Substudy B

The following contraceptive methods are appropriate for WOCBP participating in Substudy B:

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

Other Effective Methods

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
10. Male or female condom, with or without spermicide.
11. Cervical cap, diaphragm, or sponge with spermicide.
12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
- For participants with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).
  - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

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

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

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

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

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

10.6. Appendix 6: Kidney Safety Monitoring Guidelines

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

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

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

10.6.2. Age-Specific Kidney Function Calculation Recommendations

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

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

Inker LA et al. N Engl J Med. 2021;385:1737-49.

10.6.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May 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-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That May Qualify as SAEs

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

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

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

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

Definitions of a Medical Device Deficiency

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

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

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.2.2) for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (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.

10.8.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 3 (Section 10.3.2).
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
USADE Definition
• A USADE (also identified as UADE in US Regulations 21 CFR 813.3) is a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

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

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

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

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

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

Follow-Up of Medical Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form.
- New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the Vaccine SAE Reporting Form within 24 hours of receipt of the information, according to the requirements provided in Section 10.3.

10.8.5. Reporting of SAEs

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

10.8.6. Reporting of SADEs

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

10.9. Appendix 9: Substudy A

10.9.1. Synopsis – Substudy A

See Section 1.1.1.

10.9.2. Schema – Substudy A

See Section 1.3.1.

10.9.3. SoA – Substudy A

Table 4. Schedule of Activities – Substudy A

Visit Identifier	A101	A102	A103	Early Withdrawal	Notes
Visit Description	**Vaccination 1**	**Vaccination 2**	**Follow-Up Visit**	**Safety Follow-Up***	*** May be conducted as a telehealth visit OR site visit if a blood draw is required.**
Visit Window (Days)	**Day 1**	**28-35 Days After Vaccination 1**	**28-35 Days After Vaccination 2**	**28-35 Days After Last Vaccination**	**Day 1 = day of Vaccination 1.**
Obtain informed consent	X				See Section 10.1.3.
Assign participant number	X				See Section 6.4.
Obtain demography and medical history† data	X				† Include date of onset and resolution (if applicable).
Perform clinical assessment	X	X			Including, if indicated, a physical examination. Examinations and assessments must occur prior to vaccination. See Section 8.3.1.
Measure vital signs	X				Blood pressure and pulse rate; see Section 8.3.2.
Measure prevaccination temperature (oral or tympanic)	X	X			If ≥38°C (100.4°F), vaccination delay criteria apply. See Section 5.5.
Discuss/review contraceptive expectations (where appropriate)	X	X			See Section 10.4.
Collect details of any licensed influenza vaccine received in the prior 12 months	X				Include product name and date of administration.

Table 4. Schedule of Activities – Substudy A

Visit Identifier	A101	A102	A103	Early Withdrawal	Notes
Visit Description	Vaccination 1	Vaccination 2	Follow-Up Visit	Safety Follow-Up*	* May be conducted as a telehealth visit OR site visit if a blood draw is required.
Visit Window (Days)	Day 1	28-35 Days After Vaccination 1	28-35 Days After Vaccination 2	28-35 Days After Last Vaccination	Day 1 = day of Vaccination 1.
Collect and record nonstudy vaccine use	X‡	X¶	X¶		‡ In the previous 28 days; ¶ since the last study visit. See Section 10.9.8.7.
Collect and record prohibited medication use	X§	X**	X**		§ In the previous 60 days; ** since the last study visit. See Section 10.9.8.7.1.
Confirm eligibility	X	X			See Section 5.
Confirm that vaccination delay criteria have not been met	X	X			See Section 5.5.
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL††	See Section 10.9.10.1. †† Collection of immunogenicity samples should occur if the visit before early withdrawal included the study intervention administration.
Obtain randomization number	X				Do not randomize until eligibility is confirmed and the participant is present at the site. See Section 6.4.
Obtain study intervention allocation	X	X			See Section 6.4.
Administer study intervention	X	X			See Section 10.9.8.1.
Assess acute reactions for at least 30 minutes after study intervention administration	X	X			Must include time of onset.

Table 4. Schedule of Activities – Substudy A

Visit Identifier	A101	A102	A103	Early Withdrawal	Notes
Visit Description	Vaccination 1	Vaccination 2	Follow-Up Visit	Safety Follow-Up*	* May be conducted as a telehealth visit OR site visit if a blood draw is required.
Visit Window (Days)	Day 1	28-35 Days After Vaccination 1	28-35 Days After Vaccination 2	28-35 Days After Last Vaccination	Day 1 = day of Vaccination 1.
Explain e-diary completion requirements, provide training, assist with downloading the app, or issue provisioned device as needed	X	X			See Section 8.3.4.
Provide thermometer and measuring device	X	X‡‡			‡‡ Reissue if needed.
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	Days 1 through 7	Days 1 through 7			See Section 8.3.4.
Contact the participant reporting a severe reaction or fever in their e-diary; arrange an unscheduled visit if required	Days 1 through 7	Days 1 through 7			See Section 8.3.4.
Review the e-diary for reactions reported as present on the last day of e-diary completion and record their stop dates		X	X	X	See Section 8.3.4.
Collect the sponsor-provisioned e-diary or assist the participant with removing the study application from his or her own personal device			X	X	Ensure all e-diary data have been transferred prior to e-diary deactivation or removal of the app.
Record AEs/SAEs and obtain stop dates for previously reported events	X	X	X	X	

10.9.4. Introduction – Substudy A

10.9.4.1. Substudy A Rationale

This is a Phase 1b, single-site, parallel-group, randomized, placebo-controlled, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of RSVpreF and a modified RNA vaccine when administered as combined RSVpreF + qIRV and when administered alone.

10.9.4.2. Background

See Section 2.2.

10.9.4.3. Benefit/Risk Assessment

The risk assessments for Substudy A are addressed in Section 2.3.

Benefits to individual participants enrolled in this study may be:

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

The overall benefit/risk assessment for Substudy A is addressed in Section 2.3.3.

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

Objectives	Endpoints	Estimands
Primary Safety	**Primary Safety**	**Primary Safety**
To evaluate the safety profile of combination RSVpreF + qIRV	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions within 7 days following each vaccination • Systemic events within 7 days following each vaccination • AEs within 1 month after each vaccination • SAEs throughout the study
Primary Immunogenicity	**Primary Immunogenicity**	**Primary Immunogenicity**
To describe the immune responses elicited by combination RSVpreF + qIRV in comparison with those elicited by RSVpreF alone	• RSV A and RSV B NTs	In participants in compliance with the key protocol criteria (evaluable participants): • GMR of NTs for each RSV subgroup (A or B) 1 month after vaccination with combination RSVpreF + qIRV to that with RSVpreF alone (sequential-administration group, Visit A103)
To describe the immune responses elicited by combination RSVpreF + qIRV in comparison with those elicited by qIRV alone	• Strain-specific HAI titers for the current seasonal strains (2×A, 2×B) recommended by WHO for recombinant or cell-based influenza vaccines	In participants in compliance with the key protocol criteria (evaluable participants): • GMR of strain-specific HAI titers 1 month after vaccination with combination RSVpreF + qIRV to that with qIRV alone (sequential-administration group, Visit A102)

Objectives	Endpoints	Estimands
Exploratory	**Exploratory**	**Exploratory**
To further describe the immune responses elicited by combination RSVpreF + qIRV, by RSVpreF alone, and by qIRV alone	• RSV A and RSV B NTs • Strain-specific HAI titers	In participants in compliance with the key protocol criteria (evaluable participants): • GMTs of NTs for each RSV subgroup (A or B) at each applicable time point • GMFRs of NTs for each RSV subgroup (A or B) from before vaccination to each applicable postvaccination time point • GMTs of strain-specific HAI at each applicable time point • GMFRs of strain-specific HAI from before vaccination to each applicable postvaccination time point • The percentage of participants with strain-specific HAI titers ≥1:40 at each applicable time point • The percentage of participants achieving strain-specific HAI seroconversion[a] at each applicable postvaccination time point

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 of ≥1:10 prior to vaccination with a 4-fold rise at the time point of interest.

10.9.6. Substudy A Design

10.9.6.1. Overall Design

This study is designed to evaluate the safety, tolerability, and immunogenicity of RSVpreF and a modified RNA vaccine (qIRV) against RSV and influenza when administered as a combined vaccine and when administered alone. This 3-visit study will initially be conducted as a Phase 1b, single-site, parallel-group, randomized, placebo-controlled, observer-blinded substudy.

Approximately 250 healthy participants (n=125 per group) will be enrolled in Substudy A. Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process.

Healthy adults ≥60 years of age will be randomized 1:1 to either:

- Group 1: combination (RSVpreF + qIRV) (Visit A101) followed by placebo (Visit A102) or
- Group 2: sequential administration of qIRV (Visit A101) followed by RSVpreF (Visit A102) administered 1 month apart.

Randomization will be stratified by 3 age groups (60-64, 65-79, and ≥80 years) within each study site. To ensure a broad representation of age groups (participants at least 65 years of age) for the current recommendation on seasonal influenza vaccination, no more than 40 participants 60 through 64 years of age will be vaccinated.

Blood will be collected prior to each vaccination and at the final study visit.

Local reactions and systemic events occurring within 7 days after each vaccination will be recorded in an e-diary device or smartphone app.

AEs and SAEs will be collected from the signing of informed consent through study completion.

This study will have stopping rules that will apply to participants as specified in Section 8.3.6 with monitoring by designated unblinded sponsor site staff on an ongoing basis. If a stopping rule is confirmed as having been met, further randomization and administration of Vaccination 1 will be paused while additional information is gathered, and cumulative unblinded safety data will be reviewed by the IRC. Participants who have received Vaccination 1 will continue further study visits and procedures as scheduled. A charter for the IRC will be prepared and finalized before the first participant provides informed consent.

The IRC will review cumulative safety data from at least 10 participants who have received RSVpreF + qIRV. Concurrently, enrollment will pause until the IRC confirms a satisfactory safety assessment, whereupon enrollment will recommence.

Safety data accumulated at least 1 week following Vaccination 1 in each group will be reviewed by the sponsor's IRC to inform further development. Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, subsequent collection of blood samples from participants in that group may be halted and/or not analyzed and study visits or other procedures may be discontinued.

In the event that Substudy A is conducted immediately prior to or within the influenza season, SIIV will be offered to participants at the end of their study participation.

The total duration of Substudy A for each participant will be up to approximately 2 months. The total duration of Substudy A based on the approximate 2-month enrollment period will be approximately 4 months.

Substudy A Design

Healthy adults ≥60 years of age (125 per group, randomized 1:1)	**Visit A101 (Day 1)** **Vaccination 1**	**Visit A102 (Month 1)** 28-35 days after Vaccination 1 **Vaccination 2**	**Visit A103 (Month 2)** 28-35 days after Vaccination 2 **Follow-up**
STUDY GROUPS			
Group 1: Combination RSVpreF + qIRV / placebo	Combination (RSVpreF + qIRV)	Placebo	Blood draw
Group 2: Sequential administration qIRV / RSVpreF	qIRV	RSVpreF	Blood draw
SAFETY			
Local reactions and systemic events	Days 1 through 7	Days 1 through 7	
AEs and AESIs	Consent through study completion		48 hours
SAEs	Consent through study completion		

10.9.6.2. Scientific Rationale for Study Design

See Section 2.1.

10.9.6.3. Justification for Dose

See Section 4.3.

10.9.6.4. End of Study Definition

See Section 4.4.

10.9.7. Substudy A Population

10.9.7.1. Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into the study:

Age and Sex:

1. Participants ≥60 years of age at study enrollment.

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

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

2. Participants who are willing and able to comply with all scheduled visits, investigational plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.11.
4. Capable of giving and having signed the informed consent as described in the protocol, which includes complying with the requirements and restrictions listed in the ICD and in this protocol.
5. Receipt of licensed influenza vaccination for the 2022-2023 northern hemisphere season or 2022 southern hemisphere season >120 days before study intervention administration.

10.9.7.2. Substudy A Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

Medical Conditions:

1. A confirmed diagnosis of RSV infection or influenza ≤120 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. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate IM injection.
4. Serious chronic disorder, including metastatic malignancy, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excludes the participant from participating in the study.
5. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
6. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

7. Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before study intervention administration, or planned receipt throughout the study.

   Note: Systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent (eg, for cancer or an autoimmune disease) or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) 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. Receipt of any licensed RSV vaccine at any time prior to enrollment, or planned receipt throughout the study.
10. Receipt of any licensed influenza vaccine ≤120 days before study enrollment, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

11. Participation in other studies involving an investigational RSV or mRNA influenza vaccine at any time prior to enrollment, and thereafter until study completion, regardless of vaccine assignment.
12. Participation in any other interventional studies within 28 days before study enrollment through study completion. 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.

10.9.8. Substudy A Intervention and Concomitant Therapy

10.9.8.1. Study Intervention(s) Administered

Study interventions for Substudy A will include:

10.9.8.1.1. Group 1: Combination RSVpreF + qIRV and Placebo

Group 1: Combination (RSVpreF + qIRV) / Placebo

Intervention Name	Vaccination 1 Combination (RSVpreF + qIRV)		Vaccination 2 Placebo
Vaccine Component	RSVpreF 2 Stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B	qIRV Encoding HA of 4 strains as recommended for the influenza season (2 A strains and 2 B strains)	Placebo
Dose Formulation	RSV vaccine 120 µg/vial powder for solution for injection	Quadrivalent influenza suspension for injection, CCI mg/mL (qIRV)	0.9% Normal saline
Product for Reconstitution	Sterile water as diluent for injection (0.65 mL/syringe)	N/A	N/A
Unit Dose Strength(s)	120 µg	CCI µg	0.5 mL
Route of Administration	After combining both vaccines, a single 1-mL IM injection is given into the deltoid muscle of the nondominant arm (preferred).		0.5-mL IM injection into the deltoid muscle of the nondominant arm (preferred)
Use	Experimental		Placebo
IMP or NIMP/AxMP	IMP		IMP
Sourcing	Provided centrally by Pfizer		Provided centrally by Pfizer

Group 1: Combination (RSVpreF + qIRV) / Placebo

Intervention Name	Vaccination 1 Combination (RSVpreF + qIRV)	Vaccination 2 Placebo
Packaging and Labeling	**RSVpreF** is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. It is reconstituted with a PFS of sterile water diluent for injection (supplied). **qIRV** is supplied as CCI [redacted] Study intervention(s) will be labeled as per country requirements.	Study intervention will be supplied in a glass or plastic vial. Each vial will be labeled as per country requirements.

10.9.8.1.2. Group 2: Sequential Administration of qIRV / RSVpreF

Group 2: Sequential Administration of qIRV / RSVpreF

Intervention Name	Vaccination 1 qIRV	Vaccination 2 RSVpreF
Vaccine Component	qIRV qIRV, ie, encoding HA of 4 strains as recommended for the influenza season (2 A strains and 2 B strains)	RSVpreF 2 Stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B Sterile water as diluent for injection
Dose Formulation	Quadrivalent influenza suspension for injection, CCI mg/mL (qIRV)	RSV vaccine 120 µg/vial powder for solution for injection
Product for Reconstitution	N/A	Sterile water as diluent for injection (0.65 mL/syringe)
Unit Dose Strength(s)	CCI µg	120 µg
Route of Administration	0.5-mL IM injection into the deltoid muscle of the nondominant arm (preferred)	0.5-mL IM injection into the deltoid muscle of the nondominant arm (preferred)
Use	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by Pfizer	Provided centrally by Pfizer
Packaging and Labeling	qIRV is supplied as CCI Study intervention(s) will be labeled as per country requirements.	RSVpreF is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial. It is reconstituted with a PFS of sterile water diluent for injection (supplied). Study intervention(s) will be labeled as per country requirements.

10.9.8.1.3. Administration

See Section 6.2.1.

10.9.8.1.4. Medical Devices

See Section 6.2.2.

10.9.8.1.5. Preparation, Handling, Storage, and Accountability

See Section 6.3.

10.9.8.1.5.1. Preparation and Dispensing

See Section 6.3.1.

10.9.8.1.6. Allocation to Study Intervention

See Section 6.4.

Allocation of study intervention in Substudy A will be conducted via the IRT:

- Visit A101: Randomize the participant and then obtain the Visit A101 kit/container number assignment.
- Visit A102: Obtain the participant's Visit A102 kit/container number assignment.

10.9.8.2. Blinding

This is an observer-blinded study.

10.9.8.2.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

10.9.8.2.2. 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 between study interventions, study interventions will be administered in a manner that prevents the participants from identifying the study intervention 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 nursing/medical staff or clinic pharmacy will 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.

10.9.8.2.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Substudy A. However, sponsor staff who routinely have contact with blinded site personnel, and who are not involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site, will also remain blinded. Further, details will be provided in a data blinding plan.

10.9.8.2.4. Breaking the Blind

See Section 6.5.4.

10.9.8.3. Study Intervention Compliance

See Section 6.6.

10.9.8.4. Dose Modification

Not applicable to Substudy A.

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

See Section 6.8.

10.9.8.6. Treatment of Overdose

See Section 6.9.

10.9.8.7. Prior and Concomitant Therapy

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

- Licensed influenza vaccine, if received within the 12 months prior to enrollment.
- Any nonstudy vaccinations received from 28 days prior to study enrollment until the last study visit.

Prohibited medications listed below, if taken, will be recorded in the CRF and include start and stop dates, name of the medication, dose, unit, route, and frequency.

10.9.8.7.1. 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 (Section 7). Medications and vaccinations should not be withheld if required for a participant's medical care.

- Investigational vaccines and investigational drugs are prohibited within 28 days prior to enrollment and thereafter during the course of the study.
- Licensed or nonstudy investigational RSV vaccines are prohibited at any time prior to study enrollment and thereafter during the course of the study.
- Nonstudy investigational influenza vaccines are prohibited at any time prior to study enrollment and thereafter during the course of the study.
- Licensed influenza vaccines are prohibited ≤120 days before study intervention administration and thereafter during the course of the study.
- Nonstudy inactivated or recombinant vaccines, licensed COVID-19 vaccines, or COVID-19 vaccines authorized for temporary or emergency use are prohibited within 14 days after study intervention administration.
- Nonstudy live vaccines should not be given within 28 days prior to enrollment and thereafter during the course of the study.
- Chronic systemic treatment with known immunosuppressant medications, or radiotherapy, is prohibited within 60 days prior to enrollment thereafter during the course of the study.
- Systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days are prohibited within 28 days prior to enrollment and thereafter during the course of the study.
- Blood/plasma products or immunoglobulins are prohibited within 60 days prior to enrollment and thereafter during the course 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.

10.9.8.7.2. Permitted During the Study

- Medication other than that described as prohibited in Section 10.9.8.7.1 required for treatment of preexisting conditions or acute illness is permitted.
- Inhaled/nebulized, intra-articular, intrabursal, or topical (eg, skin, eyes, ears) corticosteroids are permitted.

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration is permitted.

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

See Section 7.

10.9.10. Substudy A Assessments and Procedures

10.9.10.1. Immunogenicity Assessments

10.9.10.1.1. Blood Collection

Blood samples (approximately 50 mL per sample) for immunogenicity assessments will be collected from all enrolled participants just prior to each study vaccination at Visit A101 and Visit A102, and at Visit A103. The total blood sampling volume for individual participants in this study is approximately 150 mL across 2 months.

Instructions for the collection and handling of blood and serum samples will be provided in the laboratory manual. The date and time of each sample will be recorded.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented, and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

10.9.10.1.2. RSV Vaccine Antibody Testing

Serum samples collected at all 3 visits will be assayed for RSV A and RSV B serum NTs.

RSV A and RSV B serum NTs will be determined and reported as the NT at each blood sampling visit.

Sample collection, processing, storage, and shipping information can be found in the laboratory manual. All assays will be performed by Pfizer and/or at a facility designated by Pfizer.

10.9.10.1.3. qIRV Immune Response Testing

Serum samples collected at Visit A101 and Visit A102 will be assayed for seasonal influenza strains (2×A, 2×B) as recommended by WHO for recombinant or cell-based influenza assays.

Immune response testing for seasonal strains (2×A, 2×B) will be assessed by strain-specific HAI antibody titers to evaluate vaccine responses.

Sample collection, processing, storage, and shipping information can be found in the laboratory manual. All assays will be performed by Pfizer and/or at a facility designated by Pfizer.

10.9.10.1.4. Exploratory Assays, Including Immunogenicity Assessments and Assay Development

Samples remaining after completion of the planned assays from blood draws may be used for additional vaccine and infectious disease-related research. Samples may also be used for assay development, standardization, qualification, and validation. This work is critical in the development, qualification, and validation of serological assays and is required by regulatory authorities for their use in the licensure of a vaccine.

10.9.10.2. Biological Samples

See Section 8.2.3.

10.9.10.3. Safety Assessments

See Section 8.3.

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

See Section 8.4.

10.9.10.5. Stopping Rules

The following stopping rules are in place for Substudy A participants, based on review of AEs, ECG, and laboratory data, and apply to Vaccination 1, Day 1 through Day 28. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule. In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and any further administration of Vaccination 1 (RSVpreF + qIRV or qIRV). The PAUSE will not apply to those participants who received Vaccination 1 prior to the stopping rule being met.

- For those participants already vaccinated, all 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 criteria occur within 28 days after receiving Vaccination 1 (RSVpreF + qIRV or qIRV).

10.9.10.5.1. Stopping Rule Criteria

If any participant vaccinated with qIRV or RSVpreF + qIRV develops:

1. A new ECG abnormality that a cardiologist judges consistent with probable or possible myocarditis or pericarditis, including:
    - Sustained atrial or ventricular arrhythmias.
    - Second-degree Mobitz Type II or worse AV block or new bundle branch block.
    - Diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis.
2. An abnormal troponin I value that is confirmed to be abnormal on repeat testing, assessed as related to study intervention by the investigator.
3. If ≥1 participant vaccinated with qIRV or RSVpreF + qIRV develops confirmed myocarditis or pericarditis.
4. If any participant vaccinated with qIRV or RSVpreF + qIRV dies.
5. If ≥1 participant vaccinated with qIRV or RSVpreF + qIRV experiences a Grade 4 unsolicited AE, or SAE of any severity, assessed as related by the investigator.
6. If ≥2 participants vaccinated with qIRV or RSVpreF + qIRV develop the same or similar Grade 3 or higher (see Section 10.3.3, Assessment of Intensity) unsolicited AE (including laboratory abnormalities, except lymphocyte count and C-reactive protein), other than myocarditis/pericarditis, assessed as related to study intervention by the investigator.

    Note that the local reactions, systemic events, and fever (Section 8.3.4) reported within 7 days from the day of administration of Vaccination 1, irrespective whether they are recorded in the e-diary or as AEs, are excluded from this stopping rule.

A charter for the IRC will be prepared and finalized before the first participant is consented.

10.9.10.6. Study Procedures

10.9.10.6.1. Visit A101 – Vaccination 1 (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign and date 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.

Study procedures should be conducted in a stepwise manner as shown below:

- Obtain written informed consent either in electronic or hard-copy format from the participant before performing any study-specific procedures.
- Assign a single participant identifier using the IRT system.
- Obtain and record the participant demography (including complete date of birth [dd-Mmm-YYYY], sex, race, racial designation, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record any medical history of clinical significance. Include date of onset and resolution (if applicable). Use best estimate if unknown.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF (Section 8.3.1).
- Measure the participant's vital signs, including blood pressure (seated) and pulse rate.
- Measure the participant's prevaccination body temperature (oral or tympanic) to ensure that the temperature is not ≥38°C.
- Discuss contraceptive use where applicable and as described in Section 5.3.1.
- Collect details (when available) of any licensed influenza vaccine received in the last 12 months prior to enrollment in the study. Include product name and date of administration.
- Record any nonstudy vaccinations received prior to Visit A101 as described in Section 10.9.8.7. Include product name and date of administration.
- Review concomitant medication use and record any medications that are prohibited, as described in Section 10.9.8.7.1.
- Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant does not meet any temporary delay criteria as described in Section 5.5.

Note: If delay criteria are met, reschedule Vaccination 1 for a later date when the reason(s) for the temporary delay have resolved. Randomization, Visit A101 study intervention assignment in the IRT, and blood collection are to be deferred until the participant returns for Vaccination 1.

- Prior to vaccination, collect a blood sample of approximately 50 mL for immunogenicity testing.
- Obtain the participant's randomization number and Visit A101 study intervention assignment using the IRT system.
- Unblinded site staff member(s) will dispense/administer the assigned study intervention into the deltoid muscle as detailed in Section 6.2.1. Please refer to the IPM for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form, if applicable.
- Explain the e-diary technology and completion requirements. Assist with installing the e-diary application onto the participant's own device or, if required, issue a sponsor-provisioned e-diary.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording oral temperature.
- Ensure that the participant is comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 through Day 7, where Day 1 is the day of Vaccination 1.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- If the participant doesn't call, the site should contact the participant to determine if an unscheduled reactogenicity visit is required.
- Request that the participant bring their completed e-diary device to the next visit.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.9.10.6.4.2).

- Record AEs and SAEs as described in Section 10.3.3 and obtain and record stop dates for previously reported events.
- Schedule an appointment for the next study visit.
- Complete the source notes and CRF.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.9.10.6.2. Visit A102 – Vaccination 2 (28-35 Days After Vaccination 1)

- 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 as an AE (Section 8.3.1).
- Measure the participant's prevaccination body temperature (oral or tympanic) to ensure that the temperature is not ≥38°C.
- Discuss contraceptive use where applicable and as described in Section 5.3.1.
- Record any nonstudy vaccinations received prior to Visit A102 as described in Section 10.9.8.7. Include product name and date of administration.
- Review concomitant medication use and record any medications that are prohibited, as described in Section 10.9.8.7.1.
- Ensure and document that all the inclusion criteria and none of the exclusion criteria are met. If the participant is no longer eligible, follow-up actions are described in Section 7.1.
- Ensure that the participant does not meet any temporary delay criteria as described in Section 5.5.

  Note: If delay criteria are met, reschedule Vaccination 2 for a later date when the reason(s) for the temporary delay have resolved. Randomization, Visit A102 study intervention assignment in the IRT, and blood collection are to be deferred until the participant returns for Vaccination 2.
- Prior to vaccination, collect a blood sample of approximately 50 mL for immunogenicity testing.
- Obtain the participant's Visit A102 study intervention assignment using the IRT system.
- Unblinded site staff member(s) will dispense/administer the assigned study intervention into the deltoid muscle as detailed in Section 6.2.1. Please refer to the IPM for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Review the e-diary technology and completion requirements. Assist with installing the e-diary application onto the participant's own device or, if required, issue a sponsor-provisioned e-diary.
- If required, reissue a measuring device to measure local reactions at the injection site and a thermometer for recording oral temperature.
- Ensure that the participant remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 through Day 7, where Day 1 is the day of Vaccination 2.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination 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.
- If the participant doesn't call, the site should contact the participant to determine if an unscheduled reactogenicity visit is required.
- Request that the participant bring their completed e-diary device to the next visit.
- Obtain stop dates for any ongoing events recorded on the last day of e-diary completion for the previous period.
- Record AEs and SAEs as described in Section 10.3.3 and obtain and record stop dates for previously reported events.
- Schedule an appointment for the next study visit.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.9.10.6.3. Visit A103 - Follow-Up Visit (28-35 Days After Vaccination 2)

- Record any nonstudy vaccinations received since the last study visit as described in Section 10.9.8.7.
- Review concomitant medication use and record any medications that are prohibited, as described in Section 10.9.8.7.1.
- Collect a blood sample of approximately 50 mL for immunogenicity.
- Review the e-diary data and obtain stop dates for any ongoing events recorded on the last day of e-diary completion for the previous period.
- Record AEs and SAEs as described in Section 10.3.3 and obtain and record stop dates for previously reported events.
- Collect the sponsor-provisioned e-diary or assist the participant with removing the study application from his or her own personal device. Ensure that all data have been transferred before deactivating the e-diary or deleting the app.
- Complete the CRF and source documents.

10.9.10.6.4. Early Withdrawals – Safety Follow-Up (28-35 Days After Last Vaccination Received)

- Safety follow-up may be conducted via a phone call, or a site visit if a blood draw is required.
- For participants who received study intervention at the visit prior to withdrawal, collect the immunogenicity 50-mL blood sample and process it as indicated in the laboratory manual.
- Review the e-diary data and obtain and record stop dates for any ongoing events recorded on the last day of e-diary completion for the previous period(s).
- Record AEs and SAEs as described in Section 10.3.3 and obtain and record stop dates for previously reported events.
- Collect the sponsor-provisioned e-diary or assist the participant with removing the study application from his or her own personal device.
- Complete the CRF and source documents.

10.9.10.6.4.1. Unscheduled Reactogenicity Visits for a Grade 3 or Suspected Grade 4 Reaction

If a **severe** local reaction (Section 8.3.4.2), **severe** systemic event (Section 8.3.4.3), or fever ≥39.0°C (≥102.1°F) (Section 8.3.4.4) is reported in the e-diary, a telephone contact with the participant should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction, systemic event, or fever is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit or referral to a healthcare facility should be scheduled as soon as possible to assess the extent of the reaction, unless:

- The participant is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error), or
- The investigator or appropriate designee determines that an unscheduled visit is not required.

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

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

The reactogenicity events should be assessed by the investigator or a medically qualified member of the site staff, such as a study physician or a study nurse, as applicable to the investigator's local practice or healthcare facility, who will:

- Measure body temperature (°C/°F).
- If present, measure the minimum and maximum diameters of redness at the injection site.
- If present, measure the minimum and maximum diameters of swelling at the injection site.
- Assess the injection site pain in accordance with the reactogenicity grading scale provided in Section 8.3.4.2.
- Assess any systemic events (fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, or new or worsened joint pain) that are present in accordance with the reactogenicity grading scale provided in Section 8.3.4.3.
- Assess for other findings associated with the reaction and record on the AE CRF, if appropriate.
- Record AEs and SAEs as described in Section 8.4.
- Complete the participant's source documents.
- The investigator or an authorized designee completes the unscheduled visit assessment CRF.

10.9.10.6.4.2. 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 Vaccination 1 must be specifically evaluated for possible myocarditis or pericarditis.

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

- ECG and
- Measurement of the troponin level

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

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

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

10.9.11. Statistical Considerations – Substudy A

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

10.9.11.1. Statistical Hypotheses

There is no statistical hypothesis in Substudy A.

The estimands corresponding to each primary, secondary, or exploratory objective are described in Section 10.9.5.

10.9.11.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled population	All participants who have a signed ICD.
Randomized population	All enrolled participants who are assigned a randomization number in the IRT system.
Safety population	All enrolled participants who receive the study intervention.

Defined Analysis Set	Description
Evaluable HAI immunogenicity population	All participants who meet the following criteria: • Are eligible for the study; • Receive the study intervention(s) to which they were randomized at Visit A101 (RSVpreF + qIRV in the combination group vs qIRV in the sequential-vaccination group); • Have the 1-month postvaccination blood collection for HAI assay within an appropriate window; • Have at least 1 valid and determinate HAI result at the 1-month postvaccination blood collection; • Have no major protocol violations from randomization through the 1-month postvaccination blood collection (through Visit A102).
Evaluable RSV immunogenicity population	All participants who meet the following criteria: • Are eligible for the study; • Receive the study intervention(s) to which they were randomized (RSVpreF + qIRV at Visit A101 for the combination group, and RSVpreF at Visit A102 for the sequential-administration group); • Have the 1-month postvaccination blood collection within an appropriate window (Visit A102 for the combination group and Visit A103 for the sequential-administration group); • Have at least 1 valid and determinate RSV NT result at the 1-month postvaccination blood collection; • Have no major protocol violations from randomization through the 1-month postvaccination blood collection.
mITT immunogenicity population	All participants who are randomized and have at least 1 valid and determinate assay result at any time point after receiving study intervention.

10.9.11.3. Statistical Analyses

Unless stated otherwise, "vaccine group" in this section refers to participants receiving **combination RSVpreF + qIRV** and participants receiving sequential administration of qIRV and RSVpreF.

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

Table 5 describes the primary endpoint statistical analysis methods.

Table 5. Primary Endpoint Analyses – Substudy A

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint after each vaccination for each vaccine group. Local reactions (redness, swelling, and pain at the injection site) and systemic events (fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, and new or worsened joint pain) from Day 1 through Day 7 after each vaccination will be presented by maximum severity and any severity. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CI (Section 9.3.1.1). • AEs and SAEs will be categorized according to MedDRA terms. All of the AEs within 1 month after each vaccination and SAEs throughout the study will be descriptively summarized with counts, percentages, and associated Clopper-Pearson 95% CI for each vaccine group (Section 9.3.1.1).
Immunogenicity	• Influenza strain-specific GMRs of HAI titers 1 month after vaccination (Visit A102 in the **combination RSVpreF + qIRV group** to Visit A103 in the sequential-administration group) and GMRs of RSV NTs 1 month after vaccination (Visit A102 in the **combination RSVpreF + qIRV group** to Visit A103 in the sequential-administration group) will be provided along with the associated 2-sided 95% CIs (Section 9.3.1.2.3).

10.9.11.3.2. Exploratory Endpoint(s)/Estimand(s) Analysis

Table 6 describes the exploratory endpoint statistical analysis methods.

Table 6. Exploratory Endpoint Analyses – Substudy A

Endpoint	Statistical Analysis Methods
Immunogenicity	• GMTs of NTs for each RSV subgroup (A or B) and GMTs of influenza strain-specific HAI titers at each applicable time point will be descriptively summarized with 2-sided 95% CIs for each vaccine group (Section 9.3.1.2.1). • GMFRs of NTs for each RSV subgroup (A or B) from before vaccination to each applicable postvaccination time point and GMFRs of influenza strain-specific HAI titers from before vaccination to each applicable postvaccination time point will be descriptively summarized with 2-sided 95% CIs for each vaccine group (Section 9.3.1.2.2). • The number and percentage of participants with strain-specific HAI titers ≥1:40 at each applicable time point and the number and percentage of participants achieving strain-specific HAI seroconversion at each applicable postvaccination time point will be summarized with 2-sided Clopper-Pearson 95% CIs for each vaccine group (Section 9.3.1.1). • The difference in the percentage of participants achieving influenza strain-specific seroconversion and strain-specific HAI titers ≥1:40 1 month after Vaccination 1 between the 2 vaccine groups will be summarized with 2-sided Miettinen and Nurminen 95% CI (Section 9.3.1.1). • Immunogenicity data may be summarized for each age stratum.

10.9.11.4. Interim Analyses

No interim analysis is planned.

10.9.11.4.1. Analysis Timing

As this is a Phase 1b study, data may be summarized when data are available for any specific objective.

One final analysis report will be performed after the last visit of the last participant when all primary and secondary endpoint data are available.

10.9.11.5. Sample Size Determination

As this substudy is not a hypothesis-testing study, the sample size was not based on study power for success.

With approximately 250 participants with a 1:1 randomization ratio, assuming a 10% nonevaluable rate, approximately 110 participants will be included in the evaluable population. With 110 evaluable participants in each group, assuming there is no difference in immune response between the combination vaccine and the individual vaccine, the probability of observing an LB of 95% CI of GMR <0.5 is provided in the table below. For any given strain/antigen, there is a <5% probability of observing that the combination vaccine is inferior to the individual vaccine with a 2-fold margin.

Antigen / Strain	Common SD (Log e Scale)[a]	Probability of Observing LB of 95% GMR <0.5 (Combination to Individual Vaccine)
RSV A	1.3	2.4%
RSV B	1.4	4.5%
H1N1	1.24	1.5%
H3N2	1.24	1.5%
B strain 1	1.24	1.5%
B strain 2	1.24	1.5%

a. The maximum SD across all age/vaccine groups from Study C3671001 was used for RSV A and RSV B. Study C4781004 assumptions were used for the SD for influenza strains.

10.10. Appendix 10: Substudy B

10.10.1. Synopsis – Substudy B

See Section 1.1.2.

10.10.2. Schema – Substudy B

See Section 1.3.2.

10.10.3. Schedule of Activities – Substudy B

Table 7. Schedule of Activities – Substudy B

Visit Identifier	B101	B102	Early Withdrawal	Notes
Visit Description	**Vaccination**	**Follow-Up Visit**	**Safety Follow-Up***	* May be conducted as a telehealth visit.
Visit Window (Days)	**Day 1**	**28-35 Days After Vaccination**		Day 1 = day of vaccination.
Obtain informed consent	X			See Section 10.1.3.
Assign participant number	X			Do not register the participant in Impala until the participant is present at the site. See Section 6.4.
Obtain demography and medical history† data	X			† Include the date of onset and date of resolution (if applicable).
Perform clinical assessment	X			Including, if indicated, a physical examination. Examinations and assessments must occur prior to vaccination. See Section 8.3.1.
Measure vital signs	X			Blood pressure and pulse rate; see Section 8.3.2.
Measure prevaccination temperature (oral or tympanic)	X			If ≥38°C (≥100.4°F), vaccination delay criteria apply. See Section 5.5.
Perform urine pregnancy test on WOCBP	X			See Sections 8.3.5 and 10.4.2.2.
Discuss/review contraceptive expectations	X			See Section 10.4.
Collect details of any licensed influenza vaccine received in the prior 18 months	X			Include product name (if known) and date of administration.

Table 7. Schedule of Activities – Substudy B

Visit Identifier	B101	B102	Early Withdrawal	Notes
Visit Description	**Vaccination**	**Follow-Up Visit**	**Safety Follow-Up***	*May be conducted as a telehealth visit.
Visit Window (Days)	**Day 1**	**28-35 Days After Vaccination**		Day 1 = day of vaccination.
Collect and record nonstudy vaccine use	X‡	X¶		‡ In the previous 28 days; ¶ since the last study visit. See Section 10.10.8.7.
Collect and record prohibited medication use	X§	X**		§ In the previous 60 days; ** since the last study visit. See Section 10.10.8.7.1.
Confirm eligibility	X			See Section 5.
Confirm that vaccination delay criteria have not been met	X			See Section 5.5.
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL		
Obtain randomization number	X			Do not randomize until eligibility is confirmed and the participant is present at the site. See Section 6.4.
Obtain study intervention allocation	X			See Section 6.4.
Administer study intervention	X			See Section 10.10.8.1.
Assess acute reactions for at least 30 minutes after study intervention administration	X			Must include time of onset.
Explain e-diary completion requirements, provide training, assist with downloading the app, or issue provisioned device as needed	X			See Section 8.3.4.
Provide thermometer and measuring device	X			

Table 7. Schedule of Activities – Substudy B

Visit Identifier	B101	B102	Early Withdrawal	Notes
Visit Description	**Vaccination**	**Follow-Up Visit**	**Safety Follow-Up***	*May be conducted as a telehealth visit.
Visit Window (Days)	**Day 1**	**28-35 Days After Vaccination**		Day 1 = day of vaccination.
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	Days 1 through 7			See Section 8.3.4.
Contact the participant reporting a severe reaction or fever in their e-diary; arrange an unscheduled visit if required	Days 1 through 7			See Section 8.3.4.
Review the e-diary for reactions reported as present on the last day of e-diary completion and record their stop dates		X	X	See Section 8.3.4.
Collect the sponsor-provisioned e-diary or assist the participant with removing the study application from his or her own personal device		X	X	Ensure that all e-diary data have been transmitted prior to e-diary deactivation or removal of the application.
Record AEs/SAEs and obtain stop dates for previously reported events	X	X	X	

10.10.4. Introduction – Substudy B

10.10.4.1. Substudy B Rationale

The development of CCI is sometimes required for injectable products to demonstrate efficacy, safety, CCI The benefits obtained CCI need to be balanced against the potential risks to tolerability.[6] CCI

The formulation development of combination vaccines requires consideration of CCI to determine whether the ultimate product achieves the desired effects in a safe and tolerable manner.[7] CCI . A prior study of healthy adults 18 to 40 years of age who received anterolateral thigh injection with 5 suspensions containing the same components as excipients of a combined pertussis–inactivated poliomyelitis–*Haemophilus influenzae* type b pediatric vaccine investigated the incidence of local pain and burning sensation.[7] CCI

This is a Phase 1b study in healthy participants ≥50 years of age. Substudy B will investigate 2 formulations of RSVpreF + qIRV of differing volumes and osmolarities. The first combination is a bedside mix of CCI , yielding a final injection volume of 1.0 mL, CCI . The second combination is a bedside mix of CCI to yield a final injection volume of 0.5 mL. The 0.5-mL CCI combination would result in CCI with the potential to influence reactogenicity at the injection site. These combinations will be evaluated for safety, tolerability, and immunogenicity, with the goal of selecting a formulation for further study.

10.10.4.2. Background

See Section 2.2.

10.10.4.3. Benefit/Risk Assessment

The risk assessments for Substudy B are addressed in Section 2.3.

Benefits to individual participants enrolled in this study may be:

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

The overall benefit/risk assessment for Substudy B is addressed in Section 2.3.3.

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

Substudy B

Objectives	Endpoints	Estimands
Primary Safety	**Primary Safety**	**Primary Safety**
To evaluate the safety profile of 2 formulations of combination RSVpreF + qIRV	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	In participants receiving the study intervention, the percentage of participants reporting: • Local reactions within 7 days following vaccination • Systemic events within 7 days following vaccination • AEs throughout the study • SAEs throughout the study
Secondary Immunogenicity	**Secondary Immunogenicity**	**Secondary Immunogenicity**
To describe the immune responses elicited by 2 formulations of combination RSVpreF + qIRV	• RSV A and RSV B NTs • Strain-specific HAI titers for the current seasonal strains (2×A, 2×B) recommended by WHO for recombinant or cell-based influenza vaccines	In participants in compliance with the key protocol criteria (evaluable participants): • GMT for each RSV subgroup (A or B) 1 month after vaccination with each formulation • GMT of HAI titers for each strain included 1 month after vaccination with each formulation

Substudy B

Objectives	Endpoints	Estimands
Exploratory	**Exploratory**	**Exploratory**
To further describe the immune responses elicited by 2 formulations of combination RSVpreF + qIRV	• RSV A and RSV B NTs • Strain-specific HAI titers	In participants in compliance with the key protocol criteria (evaluable participants): • GMTs of NTs for each RSV subgroup (A or B) before vaccination • GMFRs of NTs for each RSV subgroup (A or B) from before vaccination to 1 month after vaccination • GMTs of strain-specific HAI titers before vaccination • GMFRs of strain-specific HAI titers from before vaccination to 1 month after vaccination • The percentage of participants with strain-specific HAI titers ≥1:40 at each time point • The percentage of participants achieving strain-specific HAI seroconversion[a] 1 month 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 a 4-fold rise at the time point of interest.

10.10.6. Substudy B Design

10.10.6.1. Overall Design

Substudy B is designed to evaluate the safety, tolerability, and immunogenicity of RSVpreF and a modified RNA vaccine (qIRV) against RSV and influenza when administered as a combined vaccine in a 1.0-mL formulation and a 0.5-mL formulation. Formulations differ by osmolality and volume as described in Section 10.10.8.1.

This 2-visit study will be conducted as a Phase 1b, parallel-group, randomized, placebo-controlled, observer-blinded substudy.

Approximately 200 healthy participants (n=100 per group) will be enrolled in Substudy B. Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process.

Healthy adults ≥50 years of age will be randomized 1:1 to either:

- Group 1: combination (RSVpreF + qIRV) 1.0-mL formulation or
- Group 2: combination (RSVpreF + qIRV) 0.5-mL formulation.

Participants will be randomized by age/sex strata. Randomization will be stratified at the study site by 6 age/sex groups so that approximately 100 participants will be 50 through 64 years of age and 100 will be ≥65 years of age, in addition to having balanced sex distribution between vaccine groups. These groups are as follows:

- Females 50 through 64 years of age
- Females 65 through 79 years of age
- Females ≥80 years of age
- Males 50 through 64 years of age
- Males 65 through 79 years of age
- Males ≥80 years of age

The sentinel cohort will include approximately 20 male and female participants in the 50- through 64-year age strata only. Enrollment will be controlled such that no more than 20 participants may be vaccinated on the first day. E-diary data will be reviewed by the unblinded clinical study team members on an ongoing basis. If an imbalance of local reactions or systemic events between the sentinel-cohort groups is detected, the unblinded study team clinician will notify the IRC members, who will then determine if an IRC meeting is required to review cumulative safety data.

Vaccination of the expanded cohort will commence no sooner than 48 hours after the 20th participant in the sentinel cohort has received his or her vaccination and following review of the available safety data by the unblinded clinical study team. If no imbalance is detected in the sentinel cohort after 48 hours have passed from vaccination of the 20th participant, the site will be notified to proceed with full enrollment of the expanded cohort.

Blood will be collected prior to vaccination and at the final study visit.

Local reactions and systemic events occurring within 7 days after vaccination will be recorded in an e-diary device or smartphone application.

AEs and SAEs will be collected from the signing of informed consent through study completion.

This study will have stopping rules that will apply to participants as specified in Section 10.10.10.5 with monitoring by designated unblinded sponsor site staff on an ongoing basis. If a stopping rule is confirmed, further randomization and administration of study intervention will be paused while additional information is gathered, and cumulative unblinded safety data will be reviewed by the IRC. Participants who have received study vaccination will continue further study visits and procedures as scheduled. A charter for the IRC will be prepared and finalized before the first participant provides informed consent.

Safety data accumulated at least 1 week following vaccination in each group will be reviewed by the sponsor's IRC to inform further development. Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, subsequent collection of blood samples from participants in that group may be halted and/or not analyzed and study visits or other procedures may be discontinued.

In the event that Substudy B is conducted immediately prior to or within the influenza season, SIIV will be offered to participants at the end of their study participation.

The total duration of Substudy B for each participant will be up to approximately 1 month. The total duration of Substudy B based on the approximate 1-month enrollment period will be approximately 2 months.

10.10.6.2. Scientific Rationale for Study Design

See Section 2.1.

10.10.6.3. Justification for Dose

See Section 4.3.

10.10.6.4. End of Study Definition

See Section 4.4.

10.10.7. Substudy B Population

10.10.7.1. Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into Substudy B:

Age and Sex:

1. Participants ≥50 years of age at study enrollment.

   Refer to Section 10.4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

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

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

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.11.

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

5. Receipt of licensed influenza vaccination for the 2022-2023 northern hemisphere season or 2022 southern hemisphere season >180 days before study intervention administration.

10.10.7.2. Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

Medical Conditions

1. A confirmed diagnosis of RSV infection or influenza ≤120 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. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate IM injection.

4. Serious chronic disorder, including metastatic malignancy, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excludes the participant from participating in the study.

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

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

Prior/Concomitant Therapy

7. Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before study intervention administration, or planned receipt throughout the study.

   Note: Systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent (eg, for cancer or an autoimmune disease) or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) 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. Receipt of any RSV vaccine at any time prior to enrollment, or planned receipt throughout the study.

10. Receipt of any influenza vaccine ≤180 days before study enrollment, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience

11. Participation in other studies involving an investigational RSV vaccine or mRNA influenza vaccine at any time prior to enrollment, and thereafter until study completion, regardless of vaccine assignment.

12. Participation in any other interventional studies within 28 days before study enrollment through study completion. 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.

10.10.8. Substudy B Intervention and Concomitant Therapy

10.10.8.1. Study Intervention(s) Administered

Study interventions for Substudy B will include:

10.10.8.1.1. Group 1: Combination RSVpreF + qIRV 1.0-mL Formulation

GROUP 1	Vaccine Details		
COMBINATION 1.0 mL (RSVpreF + qIRV)	Vaccine Component	RSVpreF	qIRV
		2 Stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B	Encoding HA of 4 strains as recommended for the influenza season (2 A strains and 2 B strains)
	Dose Formulation	RSV vaccine 120 µg/vial powder for solution for injection	Quadrivalent influenza suspension for injection, CCI mg/mL (qIRV)
	Product for Reconstitution	Sterile water as diluent for injection (0.65 mL/syringe)	N/A
	Unit Dose Strength(s)	120 µg	CCI µg
	Route of Administration	After combining both vaccines, a single 1-mL IM injection is given into the deltoid muscle of the nondominant arm (preferred).	
	Use	Experimental	
	IMP or NIMP/AxMP	IMP	
	Sourcing	Provided centrally by Pfizer	
	Packaging and Labeling	**RSVpreF** is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. For the 1.0-mL formulation, the white cake is CCI [redacted] **qIRV** is supplied as CCI [redacted] Study intervention(s) will be labeled as per country requirements.	

10.10.8.1.2. Group 2: Combination RSVpreF + qIRV 0.5-mL Formulation

GROUP 2	Vaccine Details		
COMBINATION 0.5 mL (RSVpreF + qIRV)	Vaccine Component	RSVpreF	qIRV
		2 Stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B	Encoding HA of 4 strains as recommended for the influenza season (2 A strains and 2 B strains)
	Dose Formulation	RSV vaccine 120 µg/vial powder for solution for injection	Quadrivalent influenza suspension for injection, CCI mg/mL (qIRV)
	Product for Reconstitution	qIRV suspension	N/A
	Unit Dose Strength(s)	120 µg	CCI µg
	Route of Administration	After combining qIRV suspension with the RSVpreF cake, a single 0.5-mL IM injection is given into the deltoid muscle of the nondominant arm (preferred).	
	Use	Experimental	
	IMP or NIMP/AxMP	IMP	
	Sourcing	Provided centrally by Pfizer	
	Packaging and Labeling	**RSVpreF** is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. For the 0.5-mL formulation, the white cake is to be CCI [redacted] **qIRV** is supplied as CCI [redacted] Study intervention(s) will be labeled as per country requirements.	

10.10.8.1.3. Administration

See Section 6.2.1.

10.10.8.1.4. Medical Devices

See Section 6.2.2.

10.10.8.1.5. Preparation, Handling, Storage, and Accountability

See Section 6.3.

10.10.8.1.5.1. Preparation and Dispensing

See Section 6.3.1.

10.10.8.1.6. Allocation to Study Intervention

See Section 6.4.

Allocation of study intervention in Substudy B will be conducted via the IRT:

- Visit B101: Randomize the participant and then obtain the kit/container number assignment.

10.10.8.2. Blinding

This is an observer-blinded study.

10.10.8.2.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

10.10.8.2.2. 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 the administered volume and appearance differ between study interventions, study interventions will be administered in a manner that prevents the participants from identifying the study intervention based on these factors.

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 nursing/medical staff or clinic pharmacy will 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.

10.10.8.2.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Substudy B. However, sponsor staff who routinely have contact with blinded site personnel, and who are not involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site, will also remain blinded. Further, details will be provided in a data blinding plan.

10.10.8.2.4. Breaking the Blind

See Section 6.5.4.

10.10.8.3. Study Intervention Compliance

See Section 6.6.

10.10.8.4. Dose Modification

Not applicable to Substudy B.

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

See Section 6.8.

10.10.8.6. Treatment of Overdose

See Section 6.9.

10.10.8.7. Prior and Concomitant Therapy

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

- Licensed influenza vaccine received within the 18 months prior to enrollment.
- Any nonstudy vaccinations received from 28 days prior to study enrollment until the last study visit.

Prohibited medications listed below, if taken, will be recorded in the CRF and include start and stop dates, name of the medication, dose, unit, route, and frequency.

10.10.8.7.1. 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 (Section 7). Medications and vaccinations should not be withheld if required for a participant's medical care.

- Investigational vaccines and investigational drugs are prohibited within 28 days prior to enrollment and thereafter during the course of the study.

- Licensed or nonstudy investigational RSV vaccines are prohibited at any time prior to study enrollment and thereafter during the course of the study.
- Nonstudy investigational influenza vaccines are prohibited at any time prior to study enrollment and thereafter during the course of the study.
- Licensed influenza vaccines are prohibited ≤180 days before study intervention administration and thereafter during the course of the study.
- Nonstudy inactivated or recombinant vaccines, licensed COVID-19 vaccines, or COVID-19 vaccines authorized for temporary or emergency use are prohibited within 14 days after study intervention administration.
- Nonstudy live vaccines should not be given within 28 days prior to enrollment and thereafter during the course of the study.
- Chronic systemic treatment with known immunosuppressant medications, or radiotherapy, is prohibited within 60 days prior to enrollment and thereafter during the course of the study.
- Systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days are prohibited within 28 days prior to enrollment and thereafter during the course of the study.
- Blood/plasma products or immunoglobulins are prohibited within 60 days prior to enrollment and thereafter during the course 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.

10.10.8.7.2. Permitted During the Study

- Medication other than that described as prohibited in Section 10.10.8.7.1 required for the treatment of preexisting conditions or acute illness is permitted.
- Inhaled/nebulized, intra-articular, intrabursal, or topical (eg, skin, eyes, ears) corticosteroids are permitted.

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

See Section 7.

10.10.10. Substudy B Assessments and Procedures

10.10.10.1. Immunogenicity Assessments

10.10.10.1.1. Blood Collection

Blood samples (approximately 50 mL per sample) for immunogenicity assessments will be collected from all enrolled participants just prior to study vaccination at Visit B101, and at Visit B102. The total blood sampling volume for individual participants is approximately 100 mL across 1 month.

Instructions for the collection and handling of blood and serum samples will be provided in the laboratory manual. The date and time of each sample will be recorded.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

10.10.10.1.2. RSV Antigen Immunogenicity Testing

Serum samples collected at both visits will be assayed for RSV A and RSV B serum NTs.

RSV A and RSV B serum NTs will be determined and reported as the NT at each blood sampling visit.

Sample collection, processing, storage, and shipping information can be found in the laboratory manual. All assays will be performed by Pfizer and/or at a facility designated by Pfizer.

10.10.10.1.3. qIRV Strain-Specific HAI Testing

Serum samples collected at Visit B101 and Visit B102 will be assayed for seasonal influenza strains (2×A, 2×B) as recommended by WHO for recombinant or cell-based influenza assays.

Immune response testing for seasonal strains (2×A, 2×B) will be assessed by strain-specific HAI antibody titers to evaluate vaccine responses.

Sample collection, processing, storage, and shipping information can be found in the laboratory manual. All assays will be performed by Pfizer and/or at a facility designated by Pfizer.

10.10.10.1.4. Exploratory Assays, Including Immunogenicity Assessments and Assay Development

Samples remaining after completion of the planned assays from blood draws may be used for additional vaccine and infectious disease–related research. Samples may also be used for assay development, standardization, qualification, and validation. This work is critical in the development, qualification, and validation of serological assays and is required by regulatory authorities for their use in the licensure of a vaccine.

10.10.10.2. Biological Samples

See Section 8.2.3.

10.10.10.3. Safety Assessments

See Section 8.3.

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

See Section 8.4.

10.10.10.5. Stopping Rules

The following stopping rules are in place for Substudy B participants, based on review of AEs, ECG, and laboratory data, and apply to the 28-day period immediately following administration of study vaccination at Visit B101, Day 1 through Day 28. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule. In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

1. The IRC will review all appropriate data.
2. The stopping rule will PAUSE randomization and any further administration of study vaccination (Visit B101).
3. For those participants already vaccinated, all 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.

10.10.10.5.1. Stopping Rule Criteria

A stopping rule is met if any of the following criteria occur within 28 days after receiving study vaccination (Visit B101).

If any participant vaccinated with RSVpreF + qIRV develops:

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

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

2. An abnormal troponin I value that is confirmed to be abnormal on repeat testing, assessed as related to study intervention by the investigator.
3. If ≥1 participant vaccinated with RSVpreF + qIRV develops confirmed myocarditis or pericarditis.
4. If any participant vaccinated with RSVpreF + qIRV dies.
5. If ≥1 participant vaccinated with RSVpreF + qIRV experiences a Grade 4 unsolicited AE, or SAE of any severity, assessed as related to study intervention by the investigator.
6. If ≥2 participants vaccinated with RSVpreF + qIRV develop the same or similar Grade 3 or higher (see Section 10.3.3, Assessment of Intensity) unsolicited AE (including laboratory abnormalities, except lymphocyte count and C-reactive protein), other than myocarditis/pericarditis, assessed as related to study intervention by the investigator.

   Note that the local reactions, systemic events, and fever (Section 8.3.4) reported within 7 days from the day of administration of study vaccination, irrespective of whether they are recorded in the e-diary or as AEs, are excluded from this stopping rule.

A charter for the IRC will be prepared and finalized before the first participant is consented.

10.10.10.6. Study Procedures

10.10.10.6.1. Visit B101 – Vaccination (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign and date 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.

Study procedures should be conducted in a stepwise manner as shown below:

- Obtain written informed consent either in electronic or hard-copy format from the participant before performing any study-specific procedures.
- Assign a single participant identifier using the IRT system.

- Obtain and record the participant demography (including complete date of birth [dd-Mmm-YYYY], sex, race, racial designation, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record any medical history of clinical significance. Include date of onset and resolution (if applicable). Use best estimate if unknown.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF (Section 8.3.1).
- Measure the participant's vital signs, including blood pressure (seated) and pulse rate.
- Measure the participant's prevaccination body temperature (oral or tympanic) to ensure that the temperature is not ≥38°C.
- On the day of and prior to study intervention administration, perform urine pregnancy test on WOCBP as described in Section 8.3.5.
- Discuss contraceptive use where applicable and as described in Section 5.3.1.
- Collect details of any licensed influenza vaccine received in the last 18 months prior to enrollment in the study. Include product name (if known) and date of administration.
- Record any nonstudy vaccinations received prior to Visit B101 as described in Section 10.10.8.7. Include product name and date of administration.
- Review concomitant medication use and record any medications that are prohibited, as described in Section 10.10.8.7.1.
- Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant does not meet any temporary delay criteria as described in Section 5.5.

  Note: If delay criteria are met, reschedule the study vaccination for a later date when the reason(s) for the temporary delay have resolved. Randomization, Visit B101 study intervention assignment in the IRT, and blood collection are to be deferred until the participant returns for vaccination.

- On the day of and prior to study vaccination, collect a blood sample of approximately 50 mL for immunogenicity testing.
- On the day of and prior to study vaccination, obtain the participant's randomization number and Visit B101 study intervention assignment using the IRT system.

- Suitably qualified and authorized unblinded site staff member(s) will dispense the assigned kit number, prepare the study intervention, and administer the assigned study vaccination into the participant's deltoid muscle as an IM injection as detailed in Section 6.2.1. Please refer to the IPM for further instruction on this process.

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

- Explain the e-diary technology and completion requirements. Assist with installing the e-diary application onto the participant's own device or, if required, issue a sponsor-provisioned e-diary.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording oral temperature.

- Ensure that the participant is comfortable with using the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 through Day 7, where Day 1 is the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following local reactions or systemic events 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.

  If the participant does not call, the site should contact the participant to determine if an unscheduled reactogenicity visit is required.

- Request that the participant bring their completed e-diary device to the next visit.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.10.6.3.2).
- Record AEs and SAEs as described in Section 10.3.3.
- Schedule an appointment for the next study visit.
- 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.

10.10.10.6.2. Visit B102 - Follow-Up Visit (28-35 Days After Study Vaccination)

- Record any nonstudy vaccinations received since the last study visit as described in Section 10.10.8.7.
- Review concomitant medication use and record any medications that are prohibited, as described in Section 10.10.8.7.1.
- Collect a blood sample of approximately 50 mL for immunogenicity assessments.
- Review the e-diary data and obtain stop dates for any ongoing events recorded on the last day of e-diary completion for the previous period.
- Record AEs and SAEs as described in Section 10.3.3 and obtain and record stop dates for previously reported events.
- Collect the sponsor-provisioned e-diary or assist the participant with removing the study application from his or her own personal device. Ensure that all data have been transmitted before deactivating the e-diary or deleting the application.
- Complete the CRF and source documents.

10.10.10.6.3. Early Withdrawals – Safety Follow-Up

- Safety follow-up may be conducted either via a phone call or at a site visit.
- Review the e-diary data and obtain and record stop dates for any ongoing events recorded on the last day of e-diary completion for the previous period(s).
- Ensure that all e-diary data have been transmitted to the trial manager prior to deactivation. Collect the sponsor-provisioned e-diary and, if needed, assist the participant with removing the study application from his or her own personal device.
- Record AEs and SAEs as described in Section 10.3.3 and obtain and record stop dates for previously reported events.
- Complete the CRF and source documents.

10.10.10.6.3.1. Unscheduled Reactogenicity Visits for a Grade 3 or Suspected Grade 4 Reaction

If a **severe** local reaction (Section 8.3.4.2), **severe** systemic event (Section 8.3.4.3), or fever ≥39.0°C (≥102.1°F) (Section 8.3.4.4) is reported in the e-diary, a telephone contact with the participant should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction, systemic event, or fever is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit or referral to a healthcare facility should be scheduled as soon as possible to assess the extent of the reaction, unless:

- The participant is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error), or
- The investigator or appropriate designee determines that an unscheduled visit is not required.

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

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

The reactogenicity events should be assessed by the investigator or a medically qualified member of the site staff, such as a study physician or a study nurse, as applicable to the investigator's local practice or healthcare facility, who will:

- Measure body temperature (°C/°F) (if clinically indicated).
- If present, measure the minimum and maximum diameters of redness at the injection site.
- If present, measure the minimum and maximum diameters of swelling at the injection site.
- Assess the injection site pain in accordance with the reactogenicity grading scale provided in Section 8.3.4.2.
- Assess any systemic events (fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, or new or worsened joint pain) that are present in accordance with the reactogenicity grading scale provided in Section 8.3.4.3.
- Assess for other findings associated with the reaction and record on the AE CRF, if appropriate.
- Record AEs and SAEs as described in Section 8.4.
- Complete the participant's source documents.
- The investigator or an authorized designee completes the unscheduled visit assessment CRF.

10.10.10.6.3.2. 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 Vaccination 1 must be specifically evaluated for possible myocarditis or pericarditis.

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

- ECG
- Measurement of the troponin level

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

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

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

10.10.11. Statistical Considerations – Substudy B

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

10.10.11.1. Statistical Hypotheses

There is no statistical hypothesis in Substudy B.

The estimands corresponding to each primary, secondary, or exploratory objective are described in Section 10.10.5.

10.10.11.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled population	All participants who have a signed ICD.
Randomized population	All enrolled participants who are assigned a randomization number in the IRT system.
Safety population	All enrolled participants who receive the study intervention.

Defined Analysis Set	Description
Evaluable immunogenicity population	All participants who meet the following criteria: • Are eligible for the study; • Receive the study intervention to which they were randomized at Visit B101; • Have the 1-month postvaccination blood collection for serology assay testing within an appropriate window; • Have at least 1 valid and determinate assay result at the 1-month postvaccination blood collection; • Have no major protocol violations from randomization through the 1-month postvaccination blood collection (through Visit B102).
mITT immunogenicity population	All participants who are randomized and have at least 1 valid and determinate assay result after receiving study intervention.

10.10.11.3. Statistical Analyses

Unless stated otherwise, "vaccine group" in this section refers to participants receiving specific formulation of **combination RSVpreF + qIRV** vaccine.

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

Table 8 describes the primary endpoint statistical analysis methods.

Table 8. Primary Endpoint Analyses – Substudy B

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint after vaccination for each vaccine group. Local reactions (redness, swelling, and pain at the injection site) and systemic events (fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, and new or worsened joint pain) from Day 1 through Day 7 after vaccination will be presented by maximum severity and any severity. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CI (Section 9.3.1.1). • AEs and SAEs will be categorized according to MedDRA terms. All of the AEs/SAEs within 1 month after vaccination will be descriptively summarized with counts, percentages, and associated Clopper-Pearson 95% CI for each vaccine group (Section 9.3.1.1). • Data will be summarized for overall as well as by age group (50-64 years and 65 years and older).

10.10.11.3.2. Secondary and Exploratory Endpoint(s)/Estimand(s) Analysis

Table 9 describes the secondary and exploratory endpoint statistical analysis methods.

Table 9. Secondary and Exploratory Endpoint Analyses – Substudy B

Endpoint	Statistical Analysis Methods
Immunogenicity	• GMTs of NTs for each RSV subgroup (A or B) and GMTs of influenza strain-specific HAI titers at each time point will be descriptively summarized with 2-sided 95% CIs for each vaccine group (Section 9.3.1.2.1). • GMFRs of NTs for each RSV subgroup (A or B) and GMFRs of influenza strain-specific HAI titers from before vaccination to after vaccination will be descriptively summarized with 2-sided 95% CIs for each vaccine group (Section 9.3.1.2.2). • The number and percentage of participants with strain-specific HAI titers ≥1:40 at each time point, and the number and percentage of participants achieving strain-specific HAI seroconversion, will be summarized with 2-sided Clopper-Pearson 95% CIs for each vaccine group (Section 9.3.1.1). • Data will be summarized for overall as well as by age group (50-64 years and 65 years and older).

10.10.11.4. Interim Analyses

No interim analysis is planned.

10.10.11.4.1. Analysis Timing

As this is a Phase 1b study, data may be summarized when data are available for any specific objective.

One final analysis report will be performed after the last visit of the last participant when all primary and secondary endpoint data are available.

10.10.11.5. Sample Size Determination

As this substudy is not a hypothesis-testing study, the sample size was not based on study power for success.

Assuming that 65% of participants who receive the 1.0-mL formulation would report at least 1 local reaction, 50 participants per group will provide 82% power to detect a statistical increase of 25% (ie, 90%) from the 0.5-mL reconstituted formulation (Fisher exact test).

10.11. Appendix 11: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

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

Known HIV Infection

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

Known HCV Infection

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

Known HBV Infection

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

10.12. Appendix 12: Abbreviations

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

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
Al(OH)3	aluminum hydroxide
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANMAT	Argentina National Administration of Drugs, Food and Medical Devices
AV	atrioventricular
AxMP	auxiliary medicinal product
bIRV	bivalent influenza modRNA vaccine
BNT162b2	Pfizer's COVID-19 vaccine
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHF	congestive heart failure
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
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	Clinical Trials
CTIS	Clinical Trial Information System
DCT	data collection tool
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid

Abbreviation	Term
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eSAE	electronic safety adverse event
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition assay
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure

Abbreviation	Term
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IM	intramuscular
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IPAL	investigational product accountability log
IPM	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISO	International Organization for Standardization
KDIGO	Kidney Disease Improving Global Outcomes
LAIV	live attenuated influenza vaccine
LB	lower bound
LBBB	left bundle branch block
LFT	liver function test
LNP	lipid nanoparticle
LRTI	lower respiratory tract illness
LRTI-RSV	RSV-associated lower respiratory tract illness
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
mIRV	monovalent influenza modRNA vaccine
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
mRNA	messenger ribonucleic acid
mRNA-1273	mRNA-1273 SARS-CoV-2 vaccine (Moderna)
N/A	not applicable
NA	neuraminidase
NIMP	noninvestigational medicinal product

Abbreviation	Term
NT	neutralizing titer
Omi	Omicron
PFS	prefilled syringe(s)
PI	principal investigator
PPE	personal protective equipment
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QTcF	QT interval corrected by the Fridericia formula
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
RT-PCR	reverse transcription–polymerase chain reaction
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SD	standard deviation
SIIV	seasonal inactivated influenza vaccine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
ST-T	ST-segment and T-wave
SUSAR	suspected unexpected serious adverse reaction
T bili	total bilirubin

Abbreviation	Term
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
CCI [redacted]	
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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