A PHASE 1/2, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF COMBINED VACCINE CANDIDATES AGAINST INFLUENZA AND COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech SE
Study Conducted by:	Pfizer Inc.
Study Intervention Number:	PF-07926307
Study Intervention Name:	Combination COVID-19 and Influenza modRNA Vaccine
US IND Number:	28917
EU CT Number:	Not Applicable
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C5261023
Phase:	1/2
Sponsor Agent´s Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001 United States

Brief Title: A Study to Learn About Flu and COVID-19 Vaccine Responses in Healthy People

Document History

Document	Version Date
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TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1/2, Randomized, Observer-Blinded Study to Evaluate the Safety, Tolerability, and Immunogenicity of Combined Vaccine Candidates Against Influenza and COVID-19 in Healthy Individuals

Brief Title:

A Study to Learn About Flu and COVID-19 Vaccine Responses in Healthy People

Regulatory Agency Identification Number(s):

US IND Number:	28917
EU Clinical Trial (CT) Number:	Not Applicable
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C5261023
Phase:	1/2

Rationale:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza viruses often cocirculate, with a tendency to peak in winter. Future vaccination programs for SARS-CoV-2 are likely to run concurrently with annual influenza vaccination campaigns. In practice, coronavirus disease 2019 (COVID-19) vaccines may be given simultaneously with licensed influenza vaccines. Administration of vaccines against these respiratory illnesses in a single injection may increase the likelihood that persons seeking vaccination against either SARS-CoV-2 or influenza virus would opt to protect themselves against both pathogens.

Pfizer has developed and evaluated its nucleoside-modified messenger ribonucleic acid (modRNA)–based influenza vaccine in combination with the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) platform in several clinical studies, including a Phase 1/2 study (C5261001) that enrolled younger (18 through 64 years of age) and older (≥65 years of age) adults. Study C5261001 evaluated bivalent, trivalent, and quadrivalent influenza vaccines in combination with BNT162b2. The data demonstrated that up to a total mRNA dose of 90 μg in a combination of either quadrivalent influenza modRNA vaccine (qIRV) or trivalent influenza modRNA vaccine (tIRV) with BNT162b2 is well tolerated and elicited immune responses against influenza and SARS-CoV-2 vaccine antigens in participants 18 years of age and older.

Study C5261002 is an ongoing Phase 3, randomized, observer-blinded study (NCT06178991) of combination vaccine candidates, CCI, for adults 18 through 64 years of age. For the combination vaccine candidates, a total mRNA dose of CCI µg in a combination of CCI and a total mRNA dose of CCI µg in a combination of CCI, was used. The study enrolled more than 8000 adults 18 through 64 years of age. Compared to a licensed influenza vaccine, the CCI formulation elicited robust influenza A responses, including a continued trend of higher influenza A responses versus a licensed influenza vaccine, while it showed lower geometric mean titer (GMT) and seroconversion against the influenza B strain. In addition, the formulation demonstrated comparable responses against SARS-CoV-2 versus BNT162b2. No safety signals with the combination vaccine have been identified in ongoing safety data review (blinded sponsor or unblinded external data monitoring committee [EDMC] reviews).

The purpose of this study is to evaluate different dose levels of mRNA-based COVID-19 vaccine and influenza modRNA vaccine candidates, when administered alone or as a combined injection, in healthy participants 18 through 64 years of age up to a total mRNA dose level of CCI µg, and optionally participants ≥65 years of age up to a total mRNA dose level of CCI µg. Safety, tolerability, and immunogenicity will be assessed throughout in all age cohorts.

Enrollment in adults 18 through 64 years of age (Cohort 1) will occur through parallel dosing of all vaccine groups, whereas enrollment in the ≥65-year-old cohort (Cohort 2) will be initiated in a stepwise manner to enable safety data review to occur at total mRNA dose levels ≤CCI µg, prior to escalating to a total mRNA dose level up to CCI µg. In addition, stopping rules will be applied to the review of safety data in Cohort 2. As higher-dose combination COVID-19 and influenza modRNA vaccines, including a total mRNA dose of either CCI µg (n ~3000 exposed) or CCI µg (n ~300 exposed) in Study C5261002, have been given to adults 18 through 64 years of age, and these combination vaccines have been authorized to continue development following both blinded (Pfizer) and unblinded (EDMC) review of the data, stopping rules will not be applied to Cohort 1.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
To describe the safety and tolerability of the study interventions.	• Local reactions (injection site pain, injection site redness, and injection site swelling) • Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • Adverse events (AEs) • Serious adverse events (SAEs)

Overall Design:

This is a Phase 1/2, observer-blinded (sponsor–open-label) study to evaluate the safety, tolerability, and immunogenicity of vaccine candidates against COVID-19 and influenza as a combined single injection.

The study consists of 2 cohorts; Cohort 1 (Phase 2) will study dose combinations in participants 18 through 64 years of age up to a total mRNA dose level of [redacted] µg, and Cohort 2 (Phase 1) will study dose combinations in participants ≥65 years of age up to a total mRNA dose level of [redacted] µg.

Enrollment into Cohorts 1 and 2 will occur independently, and therefore may occur separately or contemporaneously. Enrollment into Cohort 2 is optional and may be initiated at the discretion of the sponsor; commencement of enrollment into Cohort 2 will be communicated to the relevant regulatory agency and ethical review committees in advance.

Enrollment of all vaccine groups in Cohort 1 will occur in parallel, whereas enrollment into Cohort 2 will be stepwise to enable safety data review to occur at total mRNA dose levels ≤[redacted] µg, prior to escalating to total mRNA dose levels up to [redacted] µg. Stopping rules will apply for Cohort 2 as detailed in the protocol.

After signing informed consent and reviewing the eligibility criteria, eligible participants will be randomized equally to one of the vaccine groups within each cohort/subcohort and receive the study intervention at Visit 1.

The study includes collection of participant-reported reactogenicity data (local reactions and systemic events) via an electronic diary (e-diary). Blood samples of approximately 20 mL will be collected for immunogenicity assessments prior to vaccination, and at 1 month and 6 months after vaccination. All AEs will be collected from informed consent signing through 1 month following study intervention administration. Adverse events of special interest (AESIs), newly diagnosed chronic medical conditions (NDCMCs), and SAEs will be collected from informed consent signing through 6 months after study intervention administration. Protocol-specified AESIs include confirmed diagnoses of myocarditis/pericarditis, menstrual disturbances, [redacted].

Number of Participants:

Up to approximately 1350 participants will be enrolled in the study.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in this clinical study following completion of the informed consent process and randomization to study intervention.

Study Population:

Key inclusion and exclusion criteria are listed below. Refer to the protocol for the full list of eligibility criteria.

Inclusion Criteria:

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

- Cohort 1: Participants 18 through 64 years of age at Visit 1 (Day 1).
- Cohort 2: Participants ≥65 years of age at Visit 1 (Day 1).
- Healthy participants who are determined by medical history, physical examination (if clinically required), and clinical judgment of the investigator to be eligible for inclusion in the study.

Exclusion Criteria:

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

- Tested positive for influenza by a local health authority–approved testing method within 180 days prior to Day 1.
- Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies used for the treatment or prevention of COVID-19/influenza or those that are considered immunosuppressive, from 60 days before study intervention administration, or planned receipt throughout the study.
- Vaccination with any investigational or licensed 2024-2025 season formulation influenza or COVID-19 vaccine.
- Treated with antiviral therapies for influenza (eg, Tamiflu) within 180 days prior to Day 1.

Study Arms and Duration:

Total duration of trial participation for each participant will be approximately 6 months.

Study Intervention(s)						
Intervention Name	tIRV/BNT162b2 (Omicron [Omi] KP.2)	BNT162b2 (Omi KP.2)	tIRV	Trivalent influenza vaccine (TIV)	Enhanced influenza vaccine (EIV)	Normal saline placebo
Targeted Influenza Strains	As recommended by World Health Organization (WHO) for CCI vaccines (2024-2025 northern hemisphere [NH] influenza season)	Not applicable (N/A)	As recommended by WHO for CCI CCI vaccines (2024-2025 NH influenza season)	As recommended by WHO for CCI vaccines (2024-2025 NH influenza season)	As recommended by WHO for CCI vaccines (2024-2025 NH influenza season)	N/A
Type	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine	Placebo
Use	Experimental	Experimental (CCI-µg, CCI-µg dose levels) Comparator (30-µg dose level)	Experimental	Comparator	Comparator	Placebo for blinding
Investigational Medicinal Product (IMP) or Noninvestigational Medicinal Product (NIMP)/Auxiliary Medicinal Product (AxMP)	IMP	IMP	IMP	IMP	IMP	IMP
Dose Formulation	Dispersion for injection	Suspension for injection	Suspension for injection	Suspension for injection	Emulsion for injection	Normal saline (0.9% sodium chloride solution for injection)

Study Intervention(s)						
Unit Dose Strength(s)	As detailed in the investigational product manual (IPM)	100 µg/mL	As detailed in the IPM	As detailed in the IPM	As detailed in the IPM	N/A
Dosage Level(s)	As shown in the protocol, and detailed in the IPM	CCI µg, CCI µg, 30 µg	tIRV 1: CCI µg tIRV 2: CCI µg tIRV 3: CCI µg	CCI µg	CCI µg	N/A
Route of Administration	Intramuscular (IM) injection	IM injection	IM injection	IM injection	IM injection	IM injection
Sourcing	tIRV and BNT162b2 (Omi KP.2) will be mixed at the site to generate tIRV/BNT162b2 (Omi KP.2) at the relevant dose-level combination. Please see the IPM for further details.	Provided by Pfizer	Monovalent influenza modRNA vaccines (mIRVs) CCI [redacted] will be mixed at the site to generate tIRV at the relevant dose-level combination. Please see the IPM for further details.	Provided by Pfizer	Provided by Pfizer	Provided by Pfizer
Packaging and Labeling		Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.		Study intervention will be provided as a glass prefilled syringe (PFS) as open-label supply. Each carton will be labeled per country requirement.	Study intervention will be provided as a glass PFS as open-label supply. Each carton will be labeled per country requirement.	Study intervention will be provided in a plastic vial as open-label supply.
Single Reference Safety Document (SRSD)	Combination COVID-19 and influenza modRNA vaccine investigator's brochure (IB)	BNT162b2 IB	Influenza modRNA vaccines IB	CCI [redacted] United States prescribing information (USPI)	CCI [redacted] USPI	N/A

Study Arm(s)

Arm Title	Arm Description
Cohort 1	
A	Participants will be administered BNT162b2 (Omi KP.2 [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
B	Participants will be administered BNT162b2 (Omi KP.2 [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
C	Participants will be administered BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
D	Participants will be administered tIRV 1 ([redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
E	Participants will be administered TIV in the right deltoid and BNT162b2 (Omi KP.2) 30 µg in the left deltoid at Visit 1 (Day 1).
F	Participants will be administered tIRV 2 [redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
G	Participants will be administered tIRV 1 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
H	Participants will be administered tIRV 2 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
I	Participants will be administered tIRV 1 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
J	Participants will be administered tIRV 3 [redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
K	Participants will be administered tIRV 2 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
L	Participants will be administered tIRV 2 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
M	Participants will be administered tIRV 3 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
N	Participants will be administered tIRV 3 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
Cohort 2	
AA	Participants will be administered BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
BB	Participants will be administered BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
CC	Participants will be administered BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
DD	Participants will be administered tIRV 1 ([redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
EE	Participants will be administered EIV in the right deltoid and BNT162b2 (Omi KP.2) 30 µg in the left deltoid at Visit 1 (Day 1).

Study Arm(s)

Arm Title	Arm Description
FF	Participants will be administered tIRV 2 [redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
GG	Participants will be administered tIRV 1 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
HH	Participants will be administered tIRV 2 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
II	Participants will be administered tIRV 1 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
JJ	Participants will be administered tIRV 3 [redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
KK	Participants will be administered tIRV 2 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
LL	Participants will be administered tIRV 2 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
MM	Participants will be administered tIRV 3 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).

Ethical Considerations:

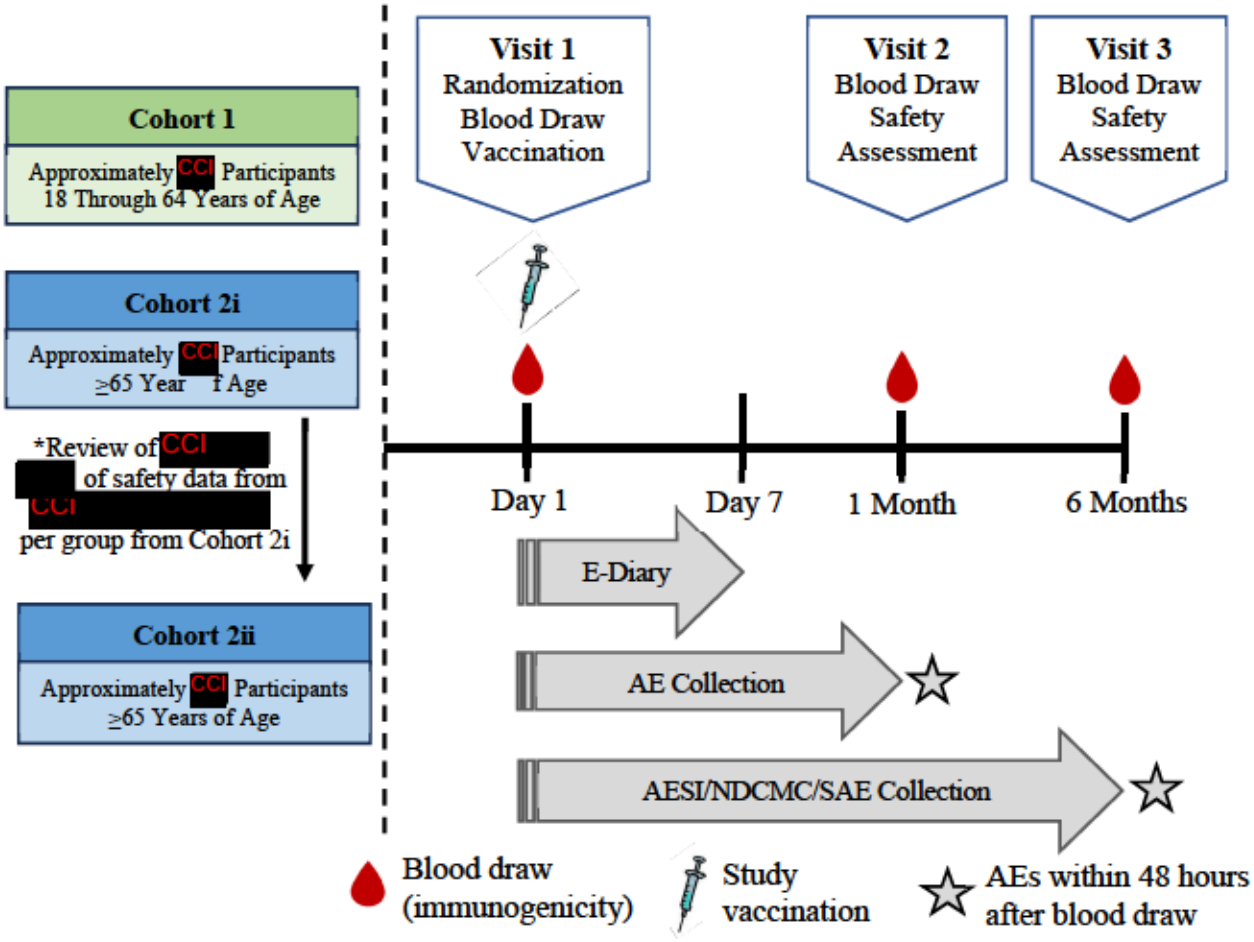
BNT162b2 shares the same manufacturing method and lipid nanoparticle composition as the investigational vaccines in this study and, due to its widespread use, globally provides a significant amount of information relating to the safety features of ribonucleic acid (RNA) vaccines. The mRNA platform is well suited to potential use in the production of influenza vaccines and combination vaccines against COVID-19 and influenza.

The available safety and immunogenicity data from ongoing clinical trials and real-world effectiveness and safety data for BNT162b2, combined with available nonclinical data with BNT162 vaccines, and the data from nonclinical and clinical trials with qIRV or tIRV alone and when in combination with BNT162b2, 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 associated with the study intervention are justified by the anticipated benefits that may be afforded to healthy participants.

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

- Local reactions, such as injection site pain, injection site redness, and injection site swelling; and systemic events, such as fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain.
- The safety profile of a novel vaccine is not yet fully characterized, so the full extent of risks is unknown.
- Very rare cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of mRNA-based COVID-19 vaccines (eg, BNT162b2).
- Venipuncture will be performed during the study. There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.
- Protection against influenza disease and COVID-19 cannot be confirmed for participants receiving investigational vaccines.
- As study participants are prohibited from receiving off-study influenza and COVID-19 vaccines, this may impact timing of when a study participant may receive seasonal vaccinations.

1.2. Schema



Note: Enrollment into Cohorts 1 and 2 will occur independently (separately or contemporaneously).
*Enrollment into Cohort 2 is at the sponsor's discretion and stepwise, with enrollment into Cohort 2ii following safety review.

1.3. Schedule of Activities

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

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

It is anticipated that the procedures below will be conducted in a stepwise manner for both Cohort 1 and Cohort 2 to ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination and after signing informed consent.

Visit Identifier	**1**	**2**	**3**	**Notes**
Visit Description	**Vaccination Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Visit**	Abbreviations used in this table may be found in Section 10.10.
Visit Mode	**Clinic**	**Clinic[a]**	**Clinic[a,b]**	
Visit Window	**Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	Day relative to administration of study intervention (Day 1).
Obtain informed consent	X			Informed consent should be obtained prior to undergoing any study-specific procedures. If vaccination is temporarily delayed, per Section 5.5, consent need not be obtained again on the day of vaccination. See Section 10.1.3 for details regarding the informed consent process.
Assign participant number	X			The participant screening number is assigned.
Obtain demographic data	X			
Obtain authorization for and perform the participant verification process via third-party vendor, if applicable	X			This study includes a participant verification process via a third-party vendor, as detailed in Section 8.1.
Medical history (including any influenza infection within the past year and/or any prior SARS-CoV-2 infection/COVID-19 diagnosis)	X			
Record last dose of COVID-19 vaccine, if received	X			Include product name (if known) in source and date of administration.

Visit Identifier	**1**	**2**	**3**	**Notes**
Visit Description	**Vaccination Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Visit**	Abbreviations used in this table may be found in Section 10.10.
Visit Mode	**Clinic**	**Clinic[a]**	**Clinic[a,b]**	
Visit Window	**Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	Day relative to administration of study intervention (Day 1).
Review and record influenza vaccinations received in the previous 3 years	X			Include product name (if known) in source and date of administration.
Record nonstudy vaccine information	X	X	X*	All vaccinations received from 28 days prior to study enrollment until the final visit.
Record prohibited medication use		X	X*	See Section 6.9.1 for a list of prohibited medications/vaccinations.
Urine pregnancy test (if appropriate)	X			See Section 8.3.5 for details regarding pregnancy testing.
Confirm use of contraceptives (if appropriate)	X			See Section 5.3.1 for details regarding the assessment of contraception use.
Measure height and weight	X			Measured prior to vaccination.
Perform a physical examination, if clinically indicated	X			Performed prior to vaccination.
Confirm eligibility	X			
Measure oral temperature	X			Measured prior to vaccination.
Review temporary delay criteria	X			See Section 5.5 for details of the temporary delay criteria.
Blood sample for immunogenicity and prior SARS-CoV-2 and/or influenza exposure assessment	~20 mL	~20 mL	~20 mL	Approximately 20 mL blood sample to be collected from all participants. Blood samples are to be taken prior to, and on same day, as study intervention on Day 1. Blood sample collection may be halted or discontinued upon notification by Pfizer, in which case Visit 3 may be conducted as a telehealth visit and safety assessments only conducted as marked "*".
Obtain randomization number using the IRT system	X			The participant randomization number is assigned (and participant allocated to a vaccine group). Do not randomize until eligibility is confirmed and no temporary delay criteria are met.
Obtain the participant's vaccine allocation using the IRT system	X			The participant vaccine allocation is assigned.

Visit Identifier	**1**	**2**	**3**	**Notes**
Visit Description	**Vaccination Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Visit**	Abbreviations used in this table may be found in Section 10.10.
Visit Mode	**Clinic**	**Clinic[a]**	**Clinic[a,b]**	
Visit Window	**Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	Day relative to administration of study intervention (Day 1).
Study intervention administration	X			See Section 6.1.1 for details regarding study intervention administration.
Assess immediate events for at least 30 minutes after study intervention administration	X			Must include time of onset. Record in the participant's source documents and on the CRF.
Explain participant communication methods (including reactogenicity e-diary completion and severe reactogenicity symptoms), assist the participant with downloading the app or issue provisioned device, if required	X			See Section 8.3.4 for details regarding completion to the study e-diary and associated grading scales. E-diary data collected for 7 days, or longer for ongoing symptoms, after study intervention administration. Day 1 of e-diary is the day of study intervention administration. **Participants are to monitor and record local reactions at the injection site on the right deltoid only within the e-diary.** Remind the participant that study staff may contact them to obtain information on symptoms entered into the e-diary until they resolve.
Provide thermometer and measuring device and provide instructions on their use	X			For daily reporting of local reaction measurements and temperature.
Ask/remind the participant to contact the site if participant experiences any severe (Grade 3) reactogenicity symptoms	X			Determine if an unscheduled reactogenicity visit is required as detailed in Section 8.3.4.5.
Ask/remind the participant to contact the site if a significant illness, medically attended event, or hospitalization occurs	X	X*		Significant illness can be new or worsening; medically attended event, eg, doctor's visit, emergency room visit.
Remind the participant to bring the e-diary device to the next visit	X			

Visit Identifier	**1**	**2**	**3**	**Notes**
Visit Description	**Vaccination Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Visit**	Abbreviations used in this table may be found in Section 10.10.
Visit Mode	**Clinic**	**Clinic[a]**	**Clinic[a,b]**	
Visit Window	**Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	Day relative to administration of study intervention (Day 1).
Site review of e-diary data with participant follow-up until ongoing event resolution	X	X*		Daily review is optimal during the active e-diary period. If a Grade 3 local reaction, systemic event, or fever is reported in the e-diary, a telephone contact must occur to ascertain further details and determine whether a site visit is clinically indicated. E-diary data are reviewed at Visit 2 with participant follow-up until ongoing symptom resolution, as applicable. Assess compliance, any medically attended events (including hospitalizations), and collect stop dates for any symptoms ongoing on the last day of the e-diary collection period (7 days). For symptoms still ongoing, continue to follow up until resolution, and document and record stop dates on the CRF.
Collect AEs, AESIs, NDCMCs, and SAEs, as appropriate	X	X*	X*	Includes nonserious AEs through Visit 2, and AESIs, NDCMCs, and SAEs through the end of study (see Section 8.4.1 for the time period in which to collect these events). In addition, any AE occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.
Assist the participant to delete the e-diary application or collect the provisioned device		X		E-diary activities for the participant are completed once the last symptom has resolved or Day 30 after vaccination, whichever occurs first (see Section 8.3.4). Ensure that all e-diary data have been transmitted prior to e-diary deactivation or removal of the application.

a. Visits may be conducted in 2 steps, where necessary (eg, where a participant cannot attend in person prior to determined deadlines; follow study team guidance): a telehealth visit to evaluate safety (activities marked with *) followed by an in-person visit to perform procedures, including collection of blood samples for immunogenicity assessments. Review of safety activities (*) should be repeated at the later in-person visit as a final assessment for each time point. Note: Both steps will need to be conducted within the visit window as per the SOA.

b. Visit 3 may be conducted as a telehealth visit and safety assessments only conducted as marked "*" if either: (1) blood sample collection has been halted or discontinued by Pfizer, or (2) the participant receives a nonstudy COVID-19 or licensed influenza vaccine after being unblinded to confirm the study intervention received after completion of Visit 2.

2. INTRODUCTION

2.1. Study Rationale

The purpose of this study is to evaluate different dose levels of mRNA-based COVID-19 vaccine and influenza modRNA vaccine candidates as a combined injection and evaluate the administration of these combination COVID-19 and influenza modRNA vaccine candidates alone in healthy participants 18 through 64 years of age up to a total mRNA dose level of [redacted] µg, and in healthy participants ≥65 years of age up to a total mRNA dose level of [redacted] µg. Safety, tolerability, and immunogenicity will be assessed throughout. Combining COVID-19 and influenza modRNA vaccines may present a number of potential advantages, including accelerated manufacturing, which would allow for later decision making for seasonal variant/strain selection. Administration of vaccines against these respiratory illnesses in a single injection may increase the likelihood that persons seeking vaccination against either SARS-CoV-2 or influenza virus would opt to protect themselves against both pathogens.[1]

2.2. Background

2.2.1. SARS-CoV-2

SARS-CoV-2, a novel b-coronavirus, is a highly transmissible and pathogenic respiratory virus responsible for the ongoing COVID-19 pandemic. Within the US, between January 2020 and August 2024, there have been over 280,000 deaths involving COVID-19 in the 18- through 64-year age group and over 900,000 deaths in those ≥65 years of age.[2] Studies of SARS-CoV-2 and SARS-CoV, a closely related coronavirus that caused the 2003 SARS outbreak, demonstrated that effective antibody protection could be achieved through spike-specific antibodies.[3,4] Therefore, vaccines targeting the spike protein of SARS-CoV-2 have been used as a critical mitigation strategy for the COVID-19 pandemic. Mutations resulting in the development of new variants may, however, reduce the efficacy of vaccines against specific strains.

The SARS-CoV-2 epidemiological landscape has been dominated by successive cycles of emergent Omicron sublineages since late 2021. XBB.1.5 had been dominant globally since February 2023; other XBB sublineages (eg, XBB.1.16, XBB.1.9.1, EG.5) continued to increase in prevalence thereafter, until the emergence and rapid predominance of JN.1 globally by January 2024.[5,6]

JN.1 remained dominant during the remainder of winter and early spring 2024. However, in February 2024, the KP.2 subvariant containing 2 new mutations (ie, F456L and R356T) that appear to confer an advantage to the virus either in terms of fitness or escape from immunity, became noticeable. By late April 2024, KP.2 had become the dominant virus variant in the US.[7] On 27 June 2024, the ACIP recommended 2024-2025 COVID-19 vaccination with a FDA-approved or authorized vaccine for all persons ≥6 months of age. On 22 August 2024, the FDA approved the 2024-2025 COVID-19 vaccine by Pfizer-BioNTech (based on the KP.2 strain) for use in persons ≥12 years of age and authorized this vaccine for use in children 6 months to 11 years of age under EUA.[8] All COVID-19 vaccines used in this study will target contemporaneous strains and/or recommended strains for inclusion in vaccines at the time the cohort is enrolled.

2.2.2. Influenza

Influenza is a major cause of morbidity and mortality worldwide, occurring in annual seasonal epidemics and occasionally in global pandemics.[9] Symptomatic influenza infection causes illness with respiratory and systemic symptoms.[10] The incidence of symptomatic influenza ranged from 2.3% through 12.9% for adults 18 through 64 years of age for the periods 2019-2020 and 2021-2022, showing the impact of this disease in this age group.[11] The risks of complications and hospitalization from influenza are higher in people ≥65 years of age.[12] Recently, for example, it is estimated that between 70% and 85% of seasonal influenza-related deaths have occurred in people 65 years and older, and between 50% and 70% of seasonal influenza-related hospitalizations have occurred among people in this age group.[13] In the US, an average of >200,000 hospitalizations per year are related to influenza,[12] while the annual global number of deaths is estimated to range from almost 300,000 to over 600,000.[14]

Influenza viruses are part of the Orthomyxoviridae family and are divided into 4 genera (3 of which are known to infect humans [A, B, and C]) based upon antigenic differences in the nucleoprotein and the matrix protein. Influenza A viruses are further classified into subtypes based upon the membrane glycoproteins, HA and NA.[15] The RNA genome is segmented, which allows genetic reassortment among viruses of the same type.[15] 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.[12] This genetic instability is what necessitates vaccines that are tailored annually.[12]

There is a recommendation in the US for routine annual influenza vaccination for all persons ≥6 months of age who do not have contraindications.[16] On 05 Mar 2024, the FDA's VRBPAC recommended that all 2024-2025 US influenza vaccines be 3-component (trivalent) vaccines and include an influenza A (H1N1), an A (H3N2), and a B/Victoria-lineage component.[17] The study design therefore will use TIVs to match this recommendation as standalone influenza vaccines and when combined with BNT162b2 (Omi KP.2).

2.2.3. Clinical Overview

2.2.3.1. SARS-CoV-2

Study C4591001 (NCT04368728) was a Phase 1/2/3 trial in ~46,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from an RNA-based vaccine candidate.[18] The trial was conducted in a heterogeneous study population: eligible participants ≥12 years of age who were healthy, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants. All doses tested for BNT162b2 ([redacted] µg, [redacted] µg, and 30 µg) in Phase 1 were safe and well tolerated. Dose levels up to 30 µg will therefore be the BNT162b2 doses being used in the present study (C5261023) when BNT162b2 is administered alone and as part of tIRV/BNT162b2.

The primary study analysis demonstrated 95.0% VE as measured in the evaluable efficacy population.

Study C4591031 – Substudy A demonstrated 95.3% relative efficacy in the boosted group, in participants 16 years of age and older, with BNT162b2 at 30 µg given ≥6 months after the primary 2-dose series provided protection against COVID-19. This was shown in participants irrespective of evidence of prior infection with SARS-CoV-2 and across various demographic subgroups.[19]

Study C4591054 – Substudy C is currently evaluating 30 µg of monovalent variant-adapted BNT162b2 (Omi JN.1) in approximately 200 participants ≥12 years of age and 30 µg of monovalent variant-adapted BNT162b2 (Omi KP.2) in approximately 100 participants ≥18 years of age. It is an open-label, Phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of up to 2 BNT162b2-based vaccines, each targeting a predominantly circulating SARS-CoV-2 variant, including BNT162b2 (Omi JN.1) and BNT162b2 (Omi KP.2) in healthy participants ≥12 years of age. This dose level will be the maximum BNT162b2 dose to be used in the present study (C5261023) when BNT162b2 is administered alone and as part of tIRV/BNT162b2.

For more details on these and other studies with BNT162b2, please reference the IB.

2.2.3.2. Influenza

Influenza modRNA vaccines have been evaluated in 3 Pfizer-sponsored clinical trials: Studies C4781001, C4781004, and C4781013.

Study C4781001 was a Phase 1/2 study evaluating monovalent, bivalent, and quadrivalent influenza vaccines in healthy adults 18 through 85 years of age. This dose-ranging study was performed to characterize the immunogenicity, reactogenicity, and safety of influenza modRNA vaccine candidates. The data gathered in this study demonstrated that a single dose of qIRV (30 µg or 60 µg total mRNA dose) was well tolerated and elicited immune responses against influenza in participants 18 through 85 years of age.

Study C4781004 is a pivotal Phase 3 study evaluating the first-generation quadrivalent modRNA influenza vaccine candidate (qIRV). This study dosed approximately 45,000 adults across the northern and southern hemispheres. The study evaluated doses of 30 µg and 60 µg quadrivalent modRNA influenza vaccines in adults 18 through 64 years and ≥65 years of age, respectively. Based on the randomization scheme, this reflects a safety database of over 9000 participants in each age cohort who have received a dose of influenza modRNA vaccine at each dose level. Both efficacy primary endpoints were met in the 18- through 64-year-old cohort, demonstrating NI to the licensed comparator. Both primary and end-of-season efficacy analyses considered both influenza A and B cases collectively, though the majority of cases in the 18- through 64-year-old cohort and the 2022-2023 influenza season overall were influenza A cases. Immunogenicity secondary endpoints were achieved only for A strains, but not for B strains.[20] The efficacy primary endpoint of noninferiority versus

licensed comparator vaccine was not met in adults 65 years and older, which may be due to the number of influenza cases available at the time of final analysis.[21]

Study C4781013 is an ongoing Phase 1/2 study (NCT06436703) initiated in early 2024 to evaluate different formulations of CCI. Substudy A of this Phase 2 trial enrolled approximately CCI participants 18 through 64 years of age. These participants were randomized to receive CCI formulation (CCI µg total RNA), CCI formulation (CCI µg), or licensed influenza vaccines. The CCI formulations CCI versus a licensed influenza vaccine. There were no safety signals reported. Data from Substudy B of this Phase 2 trial, which enrolled CCI adults 65 years of age and older, will become available at a later date. Substudy B also evaluates investigational CCI formulations (CCI µg total RNA), CCI formulations (CCI µg), and licensed influenza vaccines.[21]

For more details on these studies and non–Pfizer-sponsored studies with influenza modRNA vaccine, see the IB.

2.2.3.3. Combined Influenza and COVID-19 Vaccines

As reflected in other sections of this document, both SARS-CoV-2 and influenza continue to cause significant healthcare burden due to global circulation.[9,22] Vaccination remains an important means of reducing the risk of significant morbidity and mortality.[12] SARS-CoV-2 and influenza viruses often cocirculate, with a tendency to peak in winter. Coadministration of vaccines against both of these pathogens could provide significant advantages to both patients and caregivers in terms of simplifying care, and would likely generate overall higher vaccination rates for both viruses than if these vaccines were to be administered separately. This clinical development program is intended to determine if 2 modified mRNA vaccines designed to target influenza and SARS-CoV-2 can demonstrate an acceptable safety and immunogenicity profile.

Study C5261001 was a Phase 1/2 study evaluating bivalent, trivalent, and quadrivalent influenza vaccines in combination with BNT162b2 that enrolled both older (≥65 years of age) and younger (18 through 64 years of age) adults. This study evaluated mRNA-encoding influenza strains and BNT162b2 in combination up to a total mRNA dose of 90 µg. The data gathered to date in this study demonstrate that up to a total mRNA dose of 90 µg in a combination of either qIRV or tIRV with BNT162b2 is well tolerated and elicited immune responses against influenza and SARS-CoV-2 in participants 18 years of age and older.

In Study C5261001 – Substudy A, 60 participants 18 through 64 years of age have received qIRV/BNT162b2 (90 µg total mRNA). Thirty participants 18 through 64 years of age have received qIRV/BNT162b2 (up to 60 µg total mRNA). Study C5261001 –Substudy B was a Phase 1/2 study with additional safety and immunogenicity data being collected for both qIRV and tIRV in combination with BNT162b2.

Study C5261002 is an ongoing Phase 3, randomized, observer-blinded study (NCT06178991) of combination vaccine candidates, CCI, for adults 18 through 64 years of age. For the combination vaccine candidates, a total mRNA dose of CCI µg in a combination of CCI and a total mRNA dose of CCI µg in a combination of CCI was used. The study enrolled more than 8000 adults 18 through 64 years of age. Compared to a licensed influenza vaccine, the CCI formulation elicited robust influenza A responses, including a continued trend of higher influenza A responses versus a licensed influenza vaccine, while it showed lower GMT and seroconversion against the influenza B strain. In addition, the formulation demonstrated comparable responses against SARS-CoV-2 versus BNT162b2. No safety signals with the combination vaccine have been identified in an ongoing safety data review (blinded sponsor or unblinded EDMC reviews).[21]

This study will therefore use the same platform of CCI used in Studies C5261001 and C5261002 while evaluating different dose levels of mRNA-based COVID-19 vaccine and influenza modRNA vaccine candidates when combined.

In this study, enrollment of adults 18 through 64 years of age (Cohort 1) will occur through parallel dosing of all vaccine groups, whereas enrollment of adults ≥65 years of age (Cohort 2) will be initiated in a stepwise manner to enable safety data review to occur at total mRNA dose levels ≤CCI µg prior to escalating to a total mRNA dose level up to CCI µg. In addition, stopping rules will be applied to the review of safety data in Cohort 2. As higher-dose combination COVID-19 and influenza modRNA vaccines, including a total mRNA dose of either CCI µg (n ~3000 exposed) or CCI µg (n ~300 exposed) in Study C5261002, have been given to adults 18 through 64 years of age, and these combination vaccines have been authorized to continue development following both blinded (Pfizer) and unblinded (EDMC) review of the data, stopping rules will not be applied to Cohort 1.

2.3. Benefit/Risk Assessment

The available safety and immunogenicity data from ongoing clinical trials and real-world effectiveness and safety data for BNT162b2, combined with available nonclinical data with BNT162 vaccines, and the data from nonclinical and clinical trials with qIRV standalone and qIRV or tIRV when in combination with BNT162b2, 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 associated with the study intervention are justified by the anticipated benefits that may be afforded to healthy participants.

Clinical investigation is justified, given:

- The threat posed by continuous new outbreaks of SARS-CoV-2 infections worldwide.
- The threat posed by the SARS-CoV-2 variants emerging worldwide.

- The potential advantages and convenience to individuals in developing a combined vaccine against SARS-CoV-2 and influenza that would align with the FDA's recommendations for an annual COVID-19 vaccination approach, similar to that for influenza.[23]

More detailed information about the known and expected benefits and risks and reasonably expected AEs of the IMP may be found in the combination COVID-19 and influenza modRNA vaccine IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs, which includes the BNT162b2 IB for BNT162b2 and the influenza modRNA vaccines IB for tIRV; as well as the CCI USPI for EIV and the CCI USPI for TIV.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): tIRV/BNT162b2, tIRV, BNT162b2		
Local reactions and systemic events from the vaccine may occur (injection site pain, injection site redness, and injection site swelling; fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) following vaccination.	These are common adverse reactions seen with other vaccines,[24] as well as BNT162b2, which is also based on mRNA. The most common events reported in a large-scale efficacy study with BNT162b2 (C4591001) were mild to moderate pain at the injection site, fatigue, and headache.[18] Study C4591031 – Substudy A, a completed Phase 3 trial in approximately 5081 participants 16 years of age and older who received a third BNT162b2 dose, demonstrated that local reactions and systemic events from the third dose were generally of low grade.[19] 1-Week follow-up reactogenicity data of >6000 participants ≥18 years of age who received qIRV in the Phase 3, C4781004 study showed most events to be mild to moderate in severity, with the most common events being pain at the injection site and fatigue. This is similar to the data in Study C5261001 – Substudy A for participants 18 through 64 years of age and ≥65 years of age receiving a combination COVID-19 and influenza modRNA vaccine, where reactogenicity was mostly mild to moderate in severity, with the most common events being pain at the injection site and fatigue.	The study employs the use of a reactogenicity e-diary in participants, which allows the investigator to monitor local reactions and systemic events in real time after vaccination through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol. All study participants will be observed for at least 30 minutes after vaccination.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
All vaccines have the same mRNA platform as the original BNT162b2; therefore, the safety profile is expected to be similar to that of BNT162b2. Key risks identified for BNT162b2, and therefore for tIRV/BNT162b2, are lymphadenopathy; hypersensitivity reactions, such as rash, pruritus, urticaria, angioedema, and anaphylaxis; and myocarditis and pericarditis.[25]	Data available from the C4591001 study (with BNT162b2) showed low incidence of severe or serious events and no clinically concerning safety observations across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status.[18] Postauthorization safety data surveillance has confirmed the safety profile observed in Study C4591001 and has resulted in identification of some additional adverse reactions (risks) as noted in the SRSD. An mRNA standalone qIRV and qIRV, tIRV, or bIRV when in combination with BNT162b2 has been evaluated in past and ongoing studies described in Section 2.2.3.2 and Section 2.2.3.3. These studies have highlighted no safety concerns to date.	AE reports will be collected from the signing of the ICD through 1 month after vaccination. SAE and NDCMC reports will be collected from the signing of the ICD through 6 months after vaccination. The protocol-defined AESIs (see Section 8.4.8) of CCI [redacted] myocarditis/pericarditis, and menstrual cycle disturbances will be collected from vaccination through 6 months after vaccination. Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. All participants will be observed for at least 30 minutes after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.3.6.
Limited data are available regarding the efficacy of tIRV/BNT162b2 (Omi KP.2) and tIRV, and participants are prohibited from receiving nonstudy COVID-19 and influenza vaccines within 28 days of study intervention administration.	There is a risk that participants may develop breakthrough influenza or COVID-19 infection during the course of the study.	Ensure that participants understand the risk and are able to make informed decisions on study participation. Specific reference is made within the ICD. From Visit 2 through study completion, participants seeking receipt of licensed influenza or COVID-19 vaccines may be unblinded to confirm the study intervention received. This may only be performed after completion of all Visit 2 procedures, including entry of safety data into the CRF (see Section 6.4.4 and Section 6.9.1). AE reports will be collected from the signing of the ICD through 1 month after vaccination. SAE and NDCMC reports will be collected from the signing of the ICD through 6 months after vaccination.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		The protocol-defined AESIs (see Section 8.4.8) of CCI [redacted] will be collected from vaccination through 6 months after vaccination. Participants are permitted to receive all standard-of-care measures if they develop influenza or COVID-19.
All injectable vaccines have the potential to cause anaphylaxis in individuals who may be sensitized to components of the vaccine.	Anaphylaxis: Frequency not known.	There is an onsite 30-minute observation period after vaccination.
Cases of myocarditis and pericarditis have been reported after authorization in recipients of mRNA-based COVID-19 vaccines (eg, BNT162b2).	Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA SARS-CoV-2 vaccines after authorization. Typically, the cases have occurred more often in younger men; after the second dose of the vaccine; and within 14 days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. In the Phase 3 study evaluating a mRNA qIRV, no cases of myocarditis or pericarditis occurred after receipt of qIRV.	Specific reference to these risks for the COVID-19 vaccine is made within the ICD, with instruction to contact a healthcare professional if they develop symptoms suggestive of myocarditis or pericarditis within 6 weeks after vaccination. AESIs of myocarditis/pericarditis will be collected from vaccination through 6 months after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.3.6.
Study Intervention(s): TIV CCI [redacted]		
Local reactions and systemic events from the vaccine may occur.	In adults 18 through 64 years of age who received CCI [redacted]	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol. All study participants will be observed for at least 30 minutes after study intervention administration.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): EIV [redacted]		
Local reactions and systemic events from the vaccine may occur.	The following summary represents the [redacted]	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol. All study participants will be observed for at least 30 minutes after study intervention administration.
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.

2.3.2. Benefit Assessment

See Section 2.3 for overall study risks. Benefits to individual participants enrolled in this study may be:

- Receipt of a potentially efficacious COVID-19 vaccine at no cost to the participants.
- Receipt of a potentially efficacious influenza vaccine at no cost to the participants.
- Contributing to research to help others.

2.3.3. 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 study interventions in both cohorts are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability of the study interventions.	• Local reactions (injection site pain, injection site redness, and injection site swelling) • Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	In participants receiving study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs from vaccination through 1 month after vaccination • SAEs from vaccination through 6 months after vaccination
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the immune responses elicited by the study interventions.	• SARS-CoV-2 Omicron KP.2–neutralizing titers	In participants complying with the key protocol criteria (evaluable immunogenicity participants): • GMTs before vaccination and at each time point after vaccination • GMFR from before vaccination to each time point after vaccination • Percentage of participants with seroresponse[a] at each time point after vaccination

Objectives	Endpoints	Estimands
	• HAI titers for the 2024-2025 NH seasonal strains recommended by WHO	In participants complying with the key protocol criteria (evaluable immunogenicity participants): • GMTs before vaccination and at each time point after vaccination • GMFRs from before vaccination to each time point after vaccination • Percentages of participants achieving HAI seroconversion[b] at each time point after vaccination • Percentage of participants with HAI titers ≥1:40 before vaccination and at each time point after vaccination
CCI [redacted]		

a. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

b. 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 minimum 4-fold rise at the time point of interest.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2, observer-blinded (sponsor–open-label) study to evaluate the safety, tolerability, and immunogenicity of vaccine candidates against COVID-19 and influenza as a combined single injection.

The study consists of 2 cohorts; Cohort 1 (Phase 2) will study dose combinations in participants 18 through 64 years of age up to a total mRNA of CCI µg, and Cohort 2 (Phase 1) will study dose combinations in participants ≥65 years of age up to a total mRNA of CCI µg. Enrollment into Cohorts 1 and 2 will occur independently, and therefore may occur separately or contemporaneously. Enrollment into Cohort 2 is optional and may be initiated at the discretion of the sponsor; commencement of enrollment into Cohort 2 will be communicated to the relevant regulatory agency and ethical review committees in advance.

Enrollment of all vaccine groups in Cohort 1 will occur in parallel, whereas enrollment into Cohort 2 will be stepwise to enable safety data review to occur at total mRNA dose levels ≤CCI µg, prior to escalating to total mRNA dose levels up to CCI µg. Stopping rules will apply for Cohort 2 as detailed in Section 8.3.8.

Cohort 1

Approximately CCI participants 18 through 64 years of age will be enrolled into Cohort 1 and randomized equally to receive the study intervention at Visit 1, with up to a total mRNA dose of CCI µg, as shown in Table 1.

Table 1. Cohort 1 Study Intervention Groups

Group	Study Intervention		Total mRNA Dose	Number of Participants
	Right Deltoid	Left Deltoid		
A	BNT162b2 (Omi KP.2) CCI µg	Placebo	CCI µg	CCI
B	BNT162b2 (Omi KP.2) CCI µg	Placebo	CCI µg	
C	BNT162b2 (Omi KP.2) CCI µg	Placebo	CCI µg	
D	tIRV 1 (CCI µg)	Placebo	CCI µg	
E	TIV	BNT162b2 (Omi KP.2) 30 µg	30 µg	
F	tIRV 2 (CCI µg)	Placebo	CCI µg	
G	tIRV 1 CCI µg)/BNT162b2 (Omi KP.2 CCI µg	Placebo	CCI µg	
H	tIRV 2 CCI µg)/BNT162b2 (Omi KP.2 CCI µg	Placebo	CCI µg	
I	tIRV 1 CCI µg)/BNT162b2 (Omi KP.2 CCI µg	Placebo	CCI µg	
J	tIRV 3 (CCI µg)	Placebo	CCI µg	
K	tIRV 2 CCI µg)/BNT162b2 (Omi KP.2 CCI µg	Placebo	CCI µg	
L	tIRV 2 CCI µg)/BNT162b2 (Omi KP.2 CCI µg	Placebo	CCI µg	
M	tIRV 3 CCI µg)/BNT162b2 (Omi KP.2 CCI µg	Placebo	CCI µg	
N	tIRV 3 CCI µg)/BNT162b2 (Omi KP.2 CCI µg	Placebo	CCI µg	

Cohort 2

Approximately CCI participants ≥65 years of age will be enrolled into 2 staggered subcohorts of Cohort 2 (Cohort 2i and 2ii) and randomized equally within each subcohort to receive the study intervention at Visit 1, as shown in Table 2. Cohort 2 enrollment will be split in this way to allow enrollment of lower total mRNA dose groups prior to higher total mRNA dose groups up to a total mRNA of CCI µg:

- **Cohort 2i**: total mRNA dose ≤CCI µg = vaccine groups AA through JJ
- **Cohort 2ii**: total mRNA dose >CCI µg to ≤CCI µg = vaccine groups KK through MM

Enrollment will commence firstly in Cohort 2i, and the sponsor will review CCI of safety data from CCI per vaccine group in Cohort 2i prior to permitting enrollment to commence in Cohort 2ii. The sponsor will then review CCI of safety data from CCI per vaccine group in Cohort 2ii before permitting enrollment of the remaining participants within Cohort 2ii. Stopping rules will apply for Cohort 2 as detailed in Section 8.3.8, and the maximum total mRNA dose for any group will be up to CCI µg.

Table 2. Cohort 2 Study Intervention Groups

Group	Study Intervention		Total mRNA Dose	Number of Participants
	Right Deltoid	Left Deltoid		
Cohort 2i				
AA	BNT162b2 (Omi KP.2) CCI µg	Placebo	CCI µg	CCI
BB	BNT162b2 (Omi KP.2) µg	Placebo	µg	
CC	BNT162b2 (Omi KP.2) CCI µg	Placebo	CCI µg	
DD	tIRV 1 (CCI µg)	Placebo	CCI µg	
EE	EIV	BNT162b2 (Omi KP.2) 30 µg	30 µg	
FF	tIRV 2 (CCI µg)	Placebo	CCI µg	
GG	tIRV 1 (CCI µg)/BNT162b2 (Omi KP.2) CCI µg	Placebo	µg	
HH	tIRV 2 (µg)/BNT162b2 (Omi KP.2) µg	Placebo	µg	
II	tIRV 1 (µg)/BNT162b2 (Omi KP.2) µg	Placebo	µg	
JJ	tIRV 3 (CCI µg)	Placebo	µg	
Cohort 2ii				
KK	tIRV 2 (CCI µg)/BNT162b2 (Omi KP.2) CCI µg	Placebo	CCI µg	CCI
LL	tIRV 2 (µg)/BNT162b2 (Omi KP.2) µg	Placebo	µg	
MM	tIRV 3 (µg)/BNT162b2 (Omi KP.2) µg	Placebo	µg	

The study includes collection of participant-reported reactogenicity data (local reactions and systemic events) via an e-diary in both cohorts. Prespecified local reaction and systemic event data will be collected after study vaccination (ie, from Day 1, the day of vaccination) through Day 7, or longer for ongoing symptoms, until symptom resolution. Participants are to monitor and record local reactions at the injection site on the right deltoid only within the e-diary. Reported Grade 3 and potential Grade 4 reactogenicity events will be assessed by the investigator or qualified person to determine unscheduled medical visit requirements.

Blood samples of approximately 20 mL will be collected from participants in both cohorts for immunogenicity assessments prior to vaccination, and at 1 month and 6 months after vaccination.

For both cohorts, all AEs will be collected from informed consent signing through 1 month following study intervention administration. AESIs, NDCMCs, and SAEs will be collected from informed consent signing through 6 months after study intervention administration. Protocol-specified AESIs include confirmed diagnoses of myocarditis/pericarditis, menstrual disturbances, CCI [redacted]

4.2. Scientific Rationale for Study Design

See Section 2.1.

4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants with different characteristics to ensure the study population is representative of the patient population that will use the study intervention in clinical practice. The diversity strategy will include sites with the potential to support the recruitment of diverse and underrepresented populations in the US.

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. The diversity strategy for this study will include the following:

- Selecting sites that have access to diverse participants within their locales.
- Educating sites about the importance of increasing diversity in clinical trials and Pfizer's commitment to diversity and inclusion.
- Continual monitoring of diverse enrollment to identify additional opportunities to include diverse populations.

4.2.2. Rationale for Comparator

The active comparators for the study are the individually approved vaccine products of Comirnaty, CCI [redacted]. Their individual safety, immunogenicity, and/or efficacy characteristics have been defined. Coadministration of these licensed vaccines follows current vaccination guidelines. Since Cohort 2 will enroll US-based participants ≥65 years of age, licensed EIV CCI [redacted] will be used as the active comparator in Cohort 2 to align with the currently recommended standard of care for this age group.

In addition, different dose levels of tIRV alone and different dose levels of BNT162b2 are included as active and investigational comparators to the investigational combination tIRV and BNT162b2 vaccines.

4.2.3. Choice of Contraception/Barrier Requirements

There is no suspicion of human teratogenicity based on the intended pharmacology of the compound, but human reproductive safety data are not available for investigational study interventions. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

The 30-µg dose level of BNT162b2 was shown to be safe and effective, and has been approved in multiple countries worldwide in the original, bivalent, and variant-adapted formulations.[25,28] This will be the maximum dose of BNT162b2 administered within the study. All doses tested for BNT162b2 (CCI [redacted] µg, CCI [redacted] µg, and 30 µg) in Phase 1 of Study C4591001 were safe and well tolerated. Dose levels up to 30 µg BNT162b2 will therefore be used in the present study (C5261023) when BNT162b2 is administered alone and as part of the combination tIRV and BNT162b2 vaccine.

The mRNA dose levels of the combination vaccine to be used in this study are based on safety and immunogenicity data obtained from ongoing and completed Phase 1 through 3 studies of combination tIRV and qIRV formulations with varying strain ratios, as well as ongoing studies assessing standalone vaccines. These studies in adults ≥18 years of age have demonstrated an acceptable safety and tolerability profile of total mRNA doses up to CCI [redacted] µg (combining COVID-19 and influenza modRNA vaccines) with mainly mild to moderate local reactions and systemic events, consistent with the safety data for BNT162b2 and qIRV or tIRV administered alone. See Section 2.2.3 for further details on prior clinical studies.

The investigational formulations are also intended to characterize the dose relationship of each of the study RNA components and how they may either optimize or interfere with antibody responses against influenza and SARS-CoV-2 viruses.

Licensed active comparators will be administered at their approved doses. The ACIP preferentially recommends the use of EIVs (high-dose or adjuvanted seasonal influenza vaccine) for seasonal influenza immunization among older adults ≥65 years of age.

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, 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, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age:

1. Cohort 1: Participants 18 through 64 years of age at Visit 1 (Day 1).

   Cohort 2: Participants ≥65 years of age at Visit 1 (Day 1).

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

Disease Characteristics:

Not applicable.

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 clinically required), and clinical judgment of the investigator to be eligible for inclusion in the study.

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

4. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Tested positive for influenza by a local health authority–approved testing method within 180 days prior to Day 1.

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

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

3. Any subtype of Guillain-Barré syndrome of any etiology, dementia, or other severe progressive neurological disease.

4. Any previous history of ischemic stroke or transient ischemic attack.

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

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

   Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.9.

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

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

9. Women who are pregnant or breastfeeding.

10. Current alcohol abuse or illicit drug use.

    Note: Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some locales.

Prior/Concomitant Therapy:

11. Receipt of systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease), or radiotherapy, within 60 days before enrollment or planned receipt through conclusion of the study.

    Note: Applies to systemic corticosteroids administered at a dose of ≥20 mg/day of prednisone or equivalent for ≥14 days. Low-dose systemic corticosteroids administered at a dose of <20 mg/day of prednisone or equivalent are permitted. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

12. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies used for the treatment or prevention of COVID-19/influenza or those that are considered immunosuppressive, from 60 days before study intervention administration, or planned receipt throughout the study.

13. Vaccination with any investigational or licensed 2024/2025 season formulation influenza or COVID-19 vaccine.

14. Treated with antiviral therapies for influenza (eg, Tamiflu) within 180 days prior to Day 1.

Prior/Concurrent Clinical Study Experience:

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

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

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

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

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use.

At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use acceptable effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued 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 SAE.

5.4.1. Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number, once eligibility criteria are met.

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

The following conditions may allow a participant to be randomized in both Cohort 1 and Cohort 2 once the conditions have resolved and the participant is otherwise eligible. Participants meeting these criteria at Visit 1 will not be randomized if enrollment has closed once the condition(s) has/have resolved:

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

- A positive influenza or SARS-CoV-2 test result (NAAT or rapid antigen test) within the previous 28 days.

- Receipt of any nonstudy vaccine (other than any investigational or licensed 2024-2025 season formulation of an influenza or COVID-19 vaccine) within 28 days before study intervention administration at Visit 1.

- Anticipated receipt of any nonstudy vaccine (other than any investigational or licensed 2024-2025 season formulation of an influenza or COVID-19 vaccine) within 28 days after study intervention administration at Visit 1.

- Receipt of short-term, high-dose systemic corticosteroids (<14 days at a dose of ≥20 mg/day of prednisone or equivalent). Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days.

  Note: Low-dose systemic corticosteroids (administered at a dose of <20 mg/day of prednisone or equivalent) are permitted. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to all investigational products and active comparators as outlined in the Study Intervention(s) table in Section 6.1.

6.1. Study Intervention(s) Administered

	Study Intervention(s)					
Intervention Name	tIRV/BNT162b2 (Omi KP.2)	BNT162b2 (Omi KP.2)	tIRV	TIV	EIV	Normal saline placebo
Targeted Influenza Strains	As recommended by WHO for [redacted] vaccines (2024-2025 NH influenza season)	N/A	As recommended by WHO for [redacted] vaccines (2024-2025 NH influenza season)	As recommended by WHO for [redacted] vaccines (2024-2025 NH influenza season)	As recommended by WHO for [redacted] vaccines (2024-2025 NH influenza season)	N/A
Type	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine	Placebo
Use	Experimental	Experimental ([redacted]-µg, [redacted]-µg dose levels) Comparator (30-µg dose level)	Experimental	Comparator	Comparator	Placebo for blinding
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP
Dose Formulation	Dispersion for injection	Suspension for injection	Suspension for injection	Suspension for injection	Emulsion for injection	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	As detailed in the IPM	100 µg/mL	As detailed in the IPM	As detailed in the IPM	As detailed in the IPM	N/A
Dosage Level(s)	As shown in Table 1 and Table 2, and detailed in the IPM	[redacted] µg, [redacted] µg, 30 µg	tIRV 1: [redacted] µg tIRV 2: [redacted] µg tIRV 3: [redacted] µg	[redacted] µg	[redacted] µg	N/A
Route of Administration	IM injection	IM injection	IM injection	IM injection	IM injection	IM injection

Study Intervention(s)						
Sourcing	tIRV and BNT162b2 (Omi KP.2) will be mixed at the site to generate tIRV/BNT162b2 (Omi KP.2) at the relevant dose-level combination. Please see the IPM for further details.	Provided by Pfizer	mIRVs CCI [redacted] will be mixed at the site to generate tIRV at the relevant dose-level combination. Please see the IPM for further details.	Provided by Pfizer	Provided by Pfizer	Provided by Pfizer
Packaging and Labeling		Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.		Study intervention will be provided as a glass PFS as open-label supply. Each carton will be labeled per country requirement.	Study intervention will be provided as a glass PFS as open-label supply. Each carton will be labeled per country requirement.	Study intervention will be provided in a plastic vial as open-label supply.
SRSD	Combination COVID-19 and influenza modRNA vaccine IB	BNT162b2 IB	Influenza modRNA vaccines IB	CCI [redacted] USPI	CCI [redacted] USPI	N/A

Study Arm(s)

Arm Title	Arm Description
Cohort 1	
A	Participants will be administered BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
B	Participants will be administered BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
C	Participants will be administered BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
D	Participants will be administered tIRV 1 ([redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
E	Participants will be administered TIV in the right deltoid and BNT162b2 (Omi KP.2) 30 µg in the left deltoid at Visit 1 (Day 1).
F	Participants will be administered tIRV 2 ([redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
G	Participants will be administered tIRV 1 ([redacted] µg)/BNT162b2 (Omi KP.2 [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
H	Participants will be administered tIRV 2 ([redacted] µg)/BNT162b2 (Omi KP.2 [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
I	Participants will be administered tIRV 1 ([redacted] µg)/BNT162b2 (Omi KP.2 [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
J	Participants will be administered tIRV 3 ([redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
K	Participants will be administered tIRV 2 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
L	Participants will be administered tIRV 2 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
M	Participants will be administered tIRV 3 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
N	Participants will be administered tIRV 3 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
Cohort 2	
AA	Participants will be administered BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
BB	Participants will be administered BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
CC	Participants will be administered BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
DD	Participants will be administered tIRV 1 ([redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
EE	Participants will be administered EIV in the right deltoid and BNT162b2 (Omi KP.2) 30 µg in the left deltoid at Visit 1 (Day 1).

Study Arm(s)

Arm Title	Arm Description
FF	Participants will be administered tIRV 2 ([redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
GG	Participants will be administered tIRV 1 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
HH	Participants will be administered tIRV 2 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
II	Participants will be administered tIRV 1 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
JJ	Participants will be administered tIRV 3 ([redacted] µg) in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
KK	Participants will be administered tIRV 2 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
LL	Participants will be administered tIRV 2 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).
MM	Participants will be administered tIRV 3 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg in the right deltoid and placebo in the left deltoid at Visit 1 (Day 1).

Table 3 below details the modRNA dose per encoded influenza strain in each tIRV.

Table 3. tIRV Strain Dosages

Strain	tIRV1 ([redacted] µg)	tIRV2 ([redacted] µg)	tIRV3 ([redacted] µg)
[redacted] (H1N1) [redacted]	[redacted] µg	[redacted] µg	[redacted] µg
[redacted] (H3N2) [redacted]	[redacted] µg	[redacted] µg	[redacted] µg
[redacted] (B/Victoria) [redacted]	[redacted] µg	[redacted] µg	[redacted] µg

Table 4 describes the vaccine details for each of the constituent parts of the modRNA-containing study interventions.

Table 4. Study Intervention Component Details

Vaccine Preparation	Influenza Strains	Vaccine Antigen(s)
PF-07966731, Influenza modRNA Suspension for Injection, 0.1 mg/mL	CCI (H1N1) CCI	CCI
PF-08010605, Influenza modRNA Suspension for Injection, 0.1 mg/mL	CCI (H3N2) CCI	
PF-07872963, Influenza modRNA Suspension for Injection, 0.1 mg/mL	CCI (B/Victoria) CCI	
PF-07302048, BNT162b2 monovalent (Omi [KP.2]) Vaccine modRNA Suspension for Injection, 0.1 mg/mL	N/A	N/A

6.1.1. Administration

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

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

Study intervention administration details will be recorded on the CRF.

Participants in both Cohort 1 and Cohort 2 will receive 2 injections, one in each deltoid, at Visit 1 as randomized in accordance with the SoA. **Injections must be administered into the deltoid muscle of the appropriate arm as per Table 1 and Table 2.**

Study intervention should be administered only by an unblinded administrator IM into the deltoid muscle in such a way as to ensure that the participants remain blinded. The volume to be administered may vary by vaccine group; full details are described in the IPM.

6.1.2. Medical Devices

EIV and TIV may be provided as a PFS and should be considered a medical device.

Instructions for medical device use are provided in the IPM.

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

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

minimum and maximum temperatures since previously documented upon return to business.

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

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

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

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

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

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

6.2.1. Preparation and Dispensing

See the IPM for instructions on how to prepare the study intervention for administration.

Study intervention should be prepared and dispensed by an unblinded, appropriately qualified, and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, pharmacist, or other trained staff member) as allowed by local, state, and institutional guidance. A second unblinded staff member will verify the preparation and dispensing.

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

6.3. Assignment to Study Intervention

An IRT will allocate (randomize) participants to vaccine group(s). 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. The IRT system will provide a confirmation report, which may contain the participant number, randomization number, and study intervention allocation assigned. This report will be provided to blinded or unblinded site personnel as appropriate based on the role/permission the user is granted and must be stored in the site's blinded or unblinded files as appropriate.

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

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

6.4. Blinding

This is an observer-blind (sponsor–open-label) study.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

From Visit 2 through study completion, participants seeking receipt of licensed influenza or COVID-19 vaccines may be unblinded to confirm the study intervention received. This may only be performed after completion of all Visit 2 procedures, including entry of safety data into the CRF (refer to Section 6.4.4.2 and Section 6.9.1).

6.4.2. Blinding of Site Personnel

Participants will be assigned to receive the study intervention according to the assigned vaccine group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention until the study is unblinded to participants at a time decided by Pfizer.

In this observer-blind study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because there may be differences in physical appearance of the study interventions, the study intervention will be administered in a manner that prevents the study 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 staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents.

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

The study will be unblinded to site personnel at a time decided by Pfizer.

6.4.3. Blinding of the Sponsor

The majority of Pfizer/BioNTech staff will be unblinded to the participant's assigned study intervention.

All laboratory testing personnel will remain blinded to study intervention assigned/received throughout the study.

As this is a sponsor–open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

6.4.4. Breaking the Blind

6.4.4.1. Emergency Blind-Break

The method for breaking the blind will be using the IRT system. 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.

6.4.4.2. Pfizer-Defined Unblinding Time Point

Unblinding at the sponsor-defined unblinding time point (refer to Section 6.4.1) is not done via the IRT system but rather through a procedure detailed in the IPM. The date and reason that the blind was broken must be recorded in the source documentation and on a form provided in the IPM.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive the 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 on 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.

The site will complete the required dosage Preparation Record located in the IPM. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

6.6. Dose Modification

Not applicable.

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

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

6.8. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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

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

6.9. Prior and Concomitant Therapy

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

- Last dose of licensed or investigational COVID-19 vaccine, if received, prior to enrollment.
- All licensed or investigational influenza vaccine received within the 3 years prior to enrollment.
- All vaccinations received from 28 days prior to study enrollment until the final visit.
- Prohibited medications listed in Section 6.9.1, if taken, with the exception of prophylactic antipyretics and other pain medication to prevent symptoms.

6.9.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward; however, it is anticipated that the participant would not be withdrawn from the study (unless documented as per Section 7.3). Medications should not be withheld if required for a participant's medical care.

- Vaccines other than study intervention administered within 28 days before and 28 days after study vaccination at Visit 1.
- Receipt of any other (nonstudy) COVID-19 vaccine from enrollment prior to Visit 2 (1-month follow-up visit).
- Receipt of any other (nonstudy) influenza vaccine from enrollment prior to Visit 2 (1-month follow-up visit).

  Note: Participants seeking receipt of licensed influenza or COVID-19 vaccines may be unblinded to confirm the study intervention received after completion of Visit 2 (the 1-month follow-up visit, including all visit procedures). The decision for nonemergency unblinding of the participant must be clearly documented. The blind should be broken using the nonemergency unblinding (non-IRT) guidance in Section 6.4.4.2. Of note, any participant who requests unblinding and who is informed that they received investigational influenza and/or COVID-19 vaccine (ie, BNT162b2 doses lower than 30 µg) should be reminded that the efficacy of these vaccines is unknown, and therefore they may wish to consider seeking doses of licensed influenza and/or COVID-19 vaccine.

If a participant does receive a nonstudy COVID-19 or licensed influenza vaccine after being unblinded to confirm the study intervention received after completion of Visit 2, blood collection at Visit 3 is not required, and Visit 3 may be conducted as a telehealth visit with safety assessments only conducted as marked "*" in the SoA.

Record nonstudy vaccinations received as detailed in Section 6.9.

- Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids*), or radiotherapy, within 60 days before enrollment through conclusion of the study.

  *Applies to systemic corticosteroids administered at a dose of ≥20 mg/day of prednisone or equivalent for ≥14 days.

- Receipt of short-term, high-dose corticosteroids administered at a dose of ≥20 mg/day of prednisone or equivalent for <14 days from 28 days prior to enrollment through 28 days after administration of the study intervention.

- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies used for the treatment or prevention of COVID-19 or influenza, or those that are considered immunosuppressive, from 60 days before study intervention administration through conclusion of the study.

- Receipt of antiviral therapy with activity against influenza or COVID-19 if administered through conclusion of the study.

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

6.9.2. Permitted During the Study

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

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

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- Reactogenicity event;
- AEs;
- Participant request;
- Investigator request;
- Select protocol deviations (including no longer meeting all the inclusion criteria or meeting 1 or more exclusion criteria).

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. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and 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 only or if the participant is also discontinuing from study procedures, further study follow-up, and/or collection of additional information (see Section 7.2.3 for further details).

7.2. Participant Discontinuation/Withdrawal From the Study

7.2.1. Discontinuation/Withdrawal From Study Procedures

If a participant has received the study intervention but should discontinue blood sample collection for immunogenicity analysis because they are no longer evaluable for immunogenicity OR if a participant refuses further blood sample collection, the participant should remain in the study to be evaluated for safety. The participant will be contacted by telephone for subsequent scheduled visits through 6 months after the study intervention administration to review concomitant vaccine receipt and prohibited medications and to record AEs, AESIs, NDCMCs, and SAEs as described in Section 8.4.1 and Section 8.4.3.

7.2.2. 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:

- Reactogenicity event;
- AEs;
- Death;
- Participant request;
- Investigator request;
- Lost to follow-up;
- Study terminated by sponsor;
- Select 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 for collection of future information, no further evaluations will be performed and no additional data will be collected, except for publicly available information (see Section 7.2.3 for further details). The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.3. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and establish whether the participant wishes to continue, if eligible to do so;

- 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). These contact attempts should be documented in the participant's medical record;

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

The investigator must obtain a signed and dated ICD before performing any study-specific procedures.

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

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

This study includes a participant verification process via a third-party vendor. This process helps ensure Pfizer clinical data quality and participant safety on trials by aiding investigational sites in the monitoring for and halting of dual enrollment of participants. Participant must sign the authorization form before the verification process is initiated. See SoA for order of activities. Refer to the vendor's research site manual for details.

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 Pfizer 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.

The total blood sampling volume for individual participants in this study is up to approximately 60 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments as needed, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

8.1.1. Telehealth Visits

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

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

In addition, if a participant has received the study intervention but should discontinue blood sample collection for immunogenicity analysis because they are no longer evaluable for immunogenicity OR if a participant refuses further blood sample collection, the participant should remain in the study to be evaluated for safety. The participant will be contacted by telephone for subsequent scheduled visits after the study intervention administration to review concomitant vaccine receipt and prohibited medications and to record AEs, AESIs, and SAEs as described in Section 8.4.1 and Section 8.4.3.

8.2. Efficacy and/or Immunogenicity Assessments

Samples will be collected at the time points specified in the SoA from all participants. Blood samples must be drawn at Visit 1 prior to randomization and prior to vaccination. The following assays will be performed:

- HAI titers for the 2024-2025 NH seasonal strains recommended; HAI assays using strains as recommended by WHO[redacted] influenza vaccines may be performed.

- SARS-CoV-2 Omicron KP.2–neutralization assay.

Additional exploratory testing for influenza or SARS-CoV-2 strains not included in the vaccine composition may be performed if assays are available.

8.2.1. Testing for SARS-CoV-2 and Influenza Exposure

The N-binding antibody test may be performed by the central laboratory on each blood sample to establish prior exposure to SARS-CoV-2 up to each time point. These data will be used for study analyses.

Additional testing to evaluate influenza infection and/or prior exposure to the influenza virus up to each time point may be performed if assays are available. These data, if generated, will be used for study participant characterization.

8.2.2. 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 DNA is performed.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

In this study, a physical examination may be performed prior to vaccination, if clinically indicated.

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

For this study, the participant's oral temperature will be measured prior to vaccination. Additionally, weight and height will be measured prior to vaccination.

Vital sign findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted.

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

8.3.3. Clinical Safety Laboratory Assessments

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

8.3.4. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application installed on a provisioned device or on the personal device of the participant. All participants will be asked to monitor and record prespecified local reactions and systemic events in an e-diary during the 7-day collection period, or longer for ongoing symptoms, after study intervention administration, where Day 1 is the day of vaccination. Participants are to monitor and record local reactions at the injection site on the **right deltoid only** within the e-diary. Participants will receive reminders to complete the e-diary on a daily basis, starting on the day of vaccination (Day 1) until symptoms are reported as resolved. The reactogenicity e-diary allows recording of these assessments each day, thus providing the accurate representation of the participant's experience.

Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal. Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals to evaluate participant compliance and as part of the ongoing safety review.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting.

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

The investigator or designee must obtain stop dates from the participant for any symptoms ongoing on the last day from Day 7 onwards until resolution. The stop dates should be documented in the source documents and the information entered on 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 and adolescent volunteers enrolled in preventive vaccine clinical trials.[24]

8.3.4.2. Local Reactions

Following vaccination (where Day 1 is the day of vaccination), the participant will be asked to assess redness, swelling, and pain at the **right deltoid injection site** and to record the symptoms in the reactogenicity e-diary daily. If a local reaction persists beyond the end of the 7-day e-diary collection period, the participant will be requested to report that information and/or any new events that develop to the investigator or the study staff.

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 5. 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 5.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact must occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. If a participant experiences a Grade 4 local reaction, the investigator must immediately notify Pfizer. A Grade 4 event will be collected on the CRF.

Table 5. Local Reaction Grading Scale

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

8.3.4.3. Systemic Events

Following vaccination (where Day 1 is the day of vaccination), the participant will be asked to assess diarrhea, vomiting, headache, fatigue/tiredness, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary daily. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6. If a systemic event persists beyond the end of the 7-day e-diary collection period, the participant will be requested to report that information and/or any new events that develop to the investigator or the study staff.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact must occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify Pfizer. A Grade 4 event will be collected on the CRF.

Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
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
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/Tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

8.3.4.4. Fever

In order to record information on fever, a digital thermometer will be given to the participant with instructions on how to measure oral temperature at home.

Temperature will be collected for 7 days, or longer, following vaccination (where Day 1 is the day of vaccination). The highest temperature for each day will be recorded in the reactogenicity e-diary. Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). In the event of a fever on the last day the diary was completed, temperature will be measured daily until the fever has resolved (1 day of temperature <38.0°C [<100.4°F]) in order to collect a stop date in the CRF.

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 7 during analysis.

If a fever of ≥39.0°C (≥102.1°F) is reported in the reactogenicity e-diary, a telephone contact must occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F), after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify Pfizer. Fevers >40.0°C (>104.0°F) will be collected on the CRF.

Table 7. Scale for Fever

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4
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)

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

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

This includes:

- redness at the injection site measuring >20 measuring device units (>10.0 cm),
- swelling at the injection site measuring >20 measuring device units (>10.0 cm),
- severe injection site pain,
- fever ≥39.0°C (≥102.1°F),

- any severe systemic event.

If a Grade 3 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever >40.0°C (>104.0°F) (Section 8.3.4.4) is reported in the reactogenicity e-diary, a telephone contact or site visit must occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the extent of the Grade 3/suspected Grade 4 reaction, unless:

- The participant is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the telephone contact, or
- The participant recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error), or
- The investigator or appropriate designee determines that the visit is not required, or
- The investigator or appropriate designee confirmed severe reactogenicity assessment via medical records and/or telehealth assessment.

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

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

8.3.5. Pregnancy Testing

Following screening, pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each dose of study intervention. A negative pregnancy test result will be required prior to receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3.6. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports symptoms that might be indicative of myocarditis or pericarditis, including:

- acute chest pain,
- shortness of breath,

- palpitations,
- or any other symptom(s) that might be indicative of myocarditis or pericarditis

within 6 weeks (42 days) after the study intervention administration should be specifically evaluated for possible myocarditis/pericarditis. Efforts should be made to perform the **evaluation within 48 to 72 hours from symptom onset**.

As part of the initial clinical evaluation, the following must be performed:

- ECG and
- Measurement of the troponin level (preferably troponin I).

A basic chemistry panel and magnesium level may be performed at the same time as the measurement of the troponin level, if appropriate in the clinical judgment of the investigator, for the evaluation of clinically significant ECG abnormalities. The results of the basic chemistry panel and magnesium level, if performed, should be included in the source documentation.

If myocarditis or pericarditis is suspected based upon the initial clinical evaluation, the participant should be evaluated by a cardiologist to determine the diagnosis and manage as appropriate.

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF. In addition to ECG and troponin level, results from the following will also be recorded in the CRF:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study.

Additional laboratory testing to evaluate for potential etiologies of myocarditis and/or pericarditis may be performed, if appropriate in the clinical judgment of the investigator, if myocarditis or pericarditis is suspected based upon the initial evaluation. The results of any additional testing for etiologies of myocarditis and/or pericarditis, if performed, should be included in the source documentation.

Any diagnosis of myocarditis or pericarditis is considered an important medical event and must be reported as an SAE (refer to Section 8.4.1.1). Other diagnoses should be recorded as AEs or SAEs, as appropriate. Refer to Section 8.4.3 for information regarding follow-up of AEs and SAEs. Refer also to Section 8.4.8.

8.3.7. Additional Procedures for Monitoring of Potential Menstrual Disturbances

Any female study participant who reports any symptoms that may indicate a disturbance of their normal menstrual bleeding (eg, heavy menstrual bleeding, amenorrhea, irregular periods) following receipt of study intervention until 6 months after the last vaccination should be specifically evaluated by the investigator. Details of the symptoms, menstrual history, and results of any investigations performed will be recorded in the CRF.

8.3.8. Stopping Rules

The following stopping rules are in place for all Cohort 2 participants within CCI after vaccination based on review of AE and e-diary reactogenicity data. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor study team in order to promptly identify and flag any event that potentially contributes to a stopping rule.

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

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

- The IRC will review all appropriate data.
- The stopping rule will pause randomization and study intervention administration in **all** Cohort 2 study intervention groups.
- For all participants already vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of the study intervention in any Cohort 2 group other than CCI CCI µg) and EE (BNT162b2 [Omi KP.2] 30 µg given concurrently with EIV) as these are already licensed comparators (refer to Section 4.1). E-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

Stopping Rule Criteria:

Targeted Cardiac Abnormalities

1. If any participant develops a confirmed clinical diagnosis of [redacted].

Death

2. If any vaccinated participant [redacted] following administration of any study intervention, irrespective of investigator assessment of relatedness.

AEs and SAEs, Including Reactogenicity Events

3. If any of the following occur after vaccination in the same study intervention group:

   - Any participant experiences an SAE of any severity, assessed as related by the investigator.
   - [redacted] Participants develop the same or similar [redacted] or higher solicited AE (prespecified; as collected in the reactogenicity e-diary) sustained for over [redacted] or [redacted] or higher unsolicited AE, assessed as related to study intervention by the investigator. The following event is excluded from this criterion:

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

   - Any participant develops an investigator-confirmed [redacted] local or systemic solicited (prespecified) AE, or fever [redacted]
   - [redacted] Participants develop the same investigator-confirmed fever [redacted]

Notes:

Stopping rule criteria exclude events confirmed by the investigator as having been entered in the e-diary in error by the participant.

The grading scales utilized for the stopping rules for local reactions and systemic events are detailed in Section 8.3.4.1. The grading scales for AEs are detailed in Section 10.3.3.

Solicited AE refers to local reactions, systemic events, and fever.

Unsolicited AE refers to any other events.

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

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 8. Device deficiencies are covered in Section 8.4.9.

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

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

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

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 2 (approximately 1 month after the participant's study vaccination).

In addition, any AE occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

AESIs, NDCMCs, and SAEs (including any diagnosis of myocarditis, pericarditis, ischemic stroke, or transient ischemic attack [see Section 8.4.1.1]) will be collected from the time the participant provides informed consent through Visit 3 (approximately 6 months after the participant’s study vaccination).

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 via PSSA.

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety via PSSA immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

Any diagnosis of the following is considered an important medical event and must be reported as an SAE:

- Myocarditis or pericarditis
- Ischemic stroke or transient ischemic attack

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 Appendix 3.

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

8.4.3. Follow-Up of AEs and SAEs

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

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.

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.

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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 participant is found to be pregnant within 28 days after receiving study intervention.
- A participant inseminates a partner within 28 days after receiving study intervention.
- A 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 family member or healthcare provider reports that they are pregnant after exposure to study intervention by needlestick injury, inhalation, or skin contact.
    - A family member or healthcare provider who has been exposed to the study intervention by needlestick injury, inhalation, or skin contact then inseminates their partner prior to or around the time of conception.

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

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety via PSSA, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after receipt of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety via PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

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

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A participant is found to be breastfeeding within 28 days after receiving study intervention.

- A 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 family member or healthcare provider who reports breastfeeding after having been exposed to study intervention by needlestick injury, inhalation, or skin contact.

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

The following events are protocol-specified AESIs and are collected from study intervention through 6 months after study intervention:

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- Confirmed diagnosis of myocarditis or pericarditis. See Section 8.3.6 for additional procedures for monitoring of potential myocarditis or pericarditis within 42 days of study vaccination.
- Potential menstrual cycle disturbances. See Section 8.3.7.

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

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

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

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

The definition of a medical device deficiency can be found in Appendix 8.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.4.1 through 8.4.4 and Appendix 3 of the protocol.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

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

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

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

Refer to Section 10.8.4 for instructions for documenting and reporting medical device deficiencies.

8.4.9.2. Regulatory Reporting Requirements for Device Deficiencies

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

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

Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

- The administration of expired study intervention;

- The administration of an incorrect study intervention;

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

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

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours via PSSA **only when associated with an SAE.**

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

Retained Research Samples for Genetics are not collected in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity

Immunogenicity assessments are described in Section 8.2.

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

There is no formal hypothesis testing. All statistical analyses will be descriptive.

9.1.1. Estimands

The estimands corresponding to the primary and exploratory objectives are described in the table in Section 3.

The estimands to evaluate the safety objective are based on the safety population. These estimands estimate vaccine safety after study intervention administration. In general, completely missing reactogenicity data (ie, all 7 days of collection are missing) will not be imputed. For partially missing reactogenicity data (eg, 1 to 6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days. Missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity populations (Section 9.2). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis, unless otherwise specified. This may be adjusted once additional data on the assay characteristics become available.

9.1.2. Multiplicity Adjustment

No multiplicity adjustment is needed for the study, as there is no statistical hypothesis.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Screened	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Safety	All participants who receive any study intervention.
Evaluable SARS-CoV-2 immunogenicity	All eligible randomized participants who receive the study intervention to which they are randomized, have at least 1 valid and determinate SARS-CoV-2–neutralizing titer result from the blood sample collected within an appropriate window at Visit 2, have no reported COVID-19 or new SARS-CoV-2 infection after Visit 1 and up to 1 month after vaccination, and have no other important protocol deviations as determined by the clinician.
Evaluable HAI immunogenicity	All eligible randomized participants who receive the study intervention to which they are randomized, have at least 1 valid and determinate HAI titer result from the blood sample collected within an appropriate window at Visit 2, have no reported influenza infection after Visit 1 and up to 1 month after vaccination, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized participants who receive the study intervention and have at least 1 valid and determinate immunogenicity result after vaccination.

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 exploratory endpoints.

9.3.1. General Considerations

All safety and immunogenicity data will be summarized separately for each cohort.

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 intervention they actually received.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity population if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they are randomized.

9.3.1.1. Analysis for Binary Data

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

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

9.3.1.2. Analysis for Continuous Data

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

9.3.1.3. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transformations of assay results, calculating the 95% CI with reference to the Student t distribution, and then exponentiating the confidence limits.

9.3.1.4. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points. GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.5. 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 data points on the left side of the step.

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

Endpoint	Statistical Analysis Methods
Safety	Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group within each cohort. Local reactions and systemic events from Day 1 through Day 7 after vaccination (where Day 1 is the day of 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% CIs. AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs from vaccination through 1 month after vaccination and SAEs from vaccination through 6 months after vaccination will be provided for each vaccine group within each cohort.

9.3.3. Tertiary/Exploratory Endpoint(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	All the below summary statistics on SARS-CoV-2 Omicron KP.2–neutralizing titers will be provided for BNT162b2 recipient groups; those on HAI titers against the seasonal strains recommended by WHO for the NH 2024-2025 influenza season will be provided for influenza vaccine (tIRV, TIV, or EIV) recipient groups. • GMTs and 2-sided 95% CIs of SARS-CoV-2 Omicron KP.2–neutralizing titers and HAI titers against the seasonal strains recommended by WHO for the NH 2024-2025 influenza season before vaccination and at each time point after vaccination will be provided by vaccine group within each cohort. Statistical methods are described in Section 9.3.1. • GMFRs of SARS-CoV-2 Omicron KP.2–neutralizing titers and HAI titers against the seasonal strains recommended by WHO for the NH 2024-2025 influenza season from before vaccination to each time point after study vaccination, along with the associated 2-sided 95% CIs, will be provided by vaccine group within each cohort. Statistical methods are described in Section 9.3.1.

Endpoint	Statistical Analysis Methods
	• The percentages of participants with seroresponse to SARS-CoV-2 Omicron KP.2 at each time point after vaccination, the percentages of participants with HAI seroconversion at each time point after vaccination, and the percentages of participants with HAI titers ≥1:40 before vaccination and at each time point after vaccination and the associated Clopper-Pearson 95% CIs will be provided by vaccine group within each cohort.
CCI	[redacted]

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is a sponsor–open-label study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in Section 9.4.1.

9.4.1. Analysis Timing

Statistical analyses will be carried out when the following data are available for the specific cohort:

- Safety and immunogenicity data through 1 month after vaccination.
- Safety and immunogenicity data through 6 months after vaccination.

Additional analyses may be conducted if required for regulatory purposes, to inform product development, and/or for program-level decisions. Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time.

9.5. Sample Size Determination

The sample size is not based on any formal hypothesis test. All statistical analyses will be descriptive.

For safety outcomes, Table 8 shows the probability of observing at least 1 AE for a given true event rate of a particular AE. For example, if the true AE rate is 2%, with approximately 50 participants in a vaccine group, there is 64% probability of observing at least 1 AE.

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

Assumed True Event Rate of an AE	N=50	N=100	N=150	N=350
0.5%	0.22	0.39	0.53	0.83
1%	0.39	0.63	0.78	0.97
2%	0.64	0.87	0.95	>0.99
3%	0.78	0.95	0.99	>0.99
4%	0.87	0.98	>0.99	>0.99
5%	0.92	>0.99	>0.99	>0.99

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation, when mandated by local regulatory process, 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.

10.1.3.1. Electronic Consent

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

10.1.3.2. Remote Consent

The informed consent process may be conducted remotely with the participant at their preferred location rather than in person at the site. There are 2 types of remote consent, both of which involve the participant not being physically present with the study investigator or delegated site staff: (1) obtaining consent with the active participation of a PI or delegated site staff during the consenting process; and (2) obtaining consent without the active participation of a PI or delegated site staff, such as a via a healthcare website or portal.

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 datasets 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 Pfizer 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.

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 and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

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 a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

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

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

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

10.1.9. Use of Medical Records

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

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

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

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

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

10.1.10. Study and Site Start and Closure

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

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

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

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

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

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

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

10.1.11. Publication Policy

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

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

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or

Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. When applicable, editorial or technical support provided by a third party and paid for by Pfizer, or provided by a Pfizer employee, may be a reportable transfer of value under the Sunshine Act for US licensed physicians or other healthcare professionals. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.12. Sponsor's Medically Qualified Individual

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

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

10.2. Appendix 2: Clinical Laboratory Tests

If appropriate, a pregnancy test will be performed at times defined in the SoA.

- Pregnancy test (β-hCG): Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC for participants who are WOCBP.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

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

10.3.1. Definition of AE

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

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

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 1 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 via PSSA to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

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

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety via PSSA.
** **EDB** is reported to Pfizer Safety via PSSA, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety via PSSA.

- 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 on 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 PSSA tool/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 Use of Medical Records for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
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 PSSA tool and in accordance with the SAE reporting requirements.

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

10.3.4. Reporting of SAEs

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

SAE Reporting to Pfizer Safety via the Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE report form is the backup method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE report form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE report form pages within the designated reporting time frames.

10.3.5. Newly Diagnosed Chronic Medical Conditions

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

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

  - Agree to use a male condom, and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak, when having sexual intercourse with a WOCBP.

  OR

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

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of inclusion criterion 1 (Age; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

A participant is eligible to participate if they are 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. Premenarchal.

2. Premenopausal with 1 of the following conditions:

    - 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 judgment will determine childbearing status and study eligibility.

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.

3. 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 (as per the reference range used by the laboratory) must also be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

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

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.

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. Male and female condoms should not be used together.

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, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

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

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat-only based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat-only based equation (see Table in Section 10.6.2.1) and by combined Screat plus Scys-based equation. When postbaseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable postbaseline comparison of eGFR changes (Screat-only based eGFR and combined Screat plus Scys eGFR).

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

10.6.2. Age-Specific Kidney Function Calculation Recommendations

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

eGFR (mL/min/1.73 m²)

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

a. Adapted from Inker et al, 2021.[29]

10.6.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at screening, baseline, and postbaseline visits. Site calculations of kidney function can be performed manually, using the age-appropriate formulas (see Section 10.6.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The US National Kidney Foundation online calculators:

- Adults (18 years and above) - 2021 CKD-EPI creatinine online calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator
- Adolescents (12 years to <18 years) - Cockcroft-Gault formula (eCrCl): https://www.kidney.org/professionals/kdoqi/gfr_calculatorCoc

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

10.6.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

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

KDIGO Albuminuria (A) Criteria	A1	A2	A3
UACR	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by >60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30-second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs
• QTcF prolongation to >500 ms. • Absolute value of QTcF >450 ms AND QTcF change from baseline >60 ms. • New ST-T changes suggestive of myocardial ischemia. • New-onset LBBB (QRS complex >120 ms). • New-onset right bundle branch block (QRS complex >120 ms). • Symptomatic bradycardia. • Asystole. • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node. • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer. • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30-second duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

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

Definitions of a Medical Device Deficiency

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

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

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

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 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 Regulation 21 CFR 813.3) is an SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. 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. • If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF. • The unblinded site staff will notify the Pfizer study team by telephone or email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency. • The Pfizer study team will capture the required information on the Medical Device Complaint form along with any associated AE (either serious or nonserious) when applicable and send to the appropriate product quality complaint group.

- If the unblinded site staff determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the unblinded site staff will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. All relevant details related to the role of the device in regard to the SAE must be included in the narrative section of the PSSA tool as outlined in Section 8.4.1.1 and Section 8.4.1.2.

- It is **not** acceptable for the unblinded site staff to send photocopies of the participant's medical records to Pfizer Safety.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 Use of Medical Records for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

- For device deficiencies, it is very important that the unblinded site staff describes any corrective or remedial actions taken to prevent recurrence of the incident.

    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.

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

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

- The investigator will also consult the IB and/or product information, for marketed products in their assessment.
- For each device deficiency, the investigator **must** document in the medical notes that they have reviewed the device deficiency and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form by the Pfizer study team.
- New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety via PSSA within 24 hours of receipt of the information, according to the requirements provided in Appendix 3.

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

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

Known HIV infection

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

Known HCV infection

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

Known HBV infection

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

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
ACIP	Advisory Committee on Immunization Practices
ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
bIRV	bivalent influenza modRNA vaccine
BMI	body mass index
BNT162b2	Pfizer-BioNTech COVID-19 vaccine
CBER	Center for Biologics Evaluation and Research (United States)
CFR	Code of Federal Regulations (United States)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CTIS	Clinical Trial Information System
DCT	data collection tool
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eConsent	electronic consent
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding

Abbreviation	Term
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eICD	electronic informed consent document
EIV	enhanced influenza vaccine
eSAE	electronic serious adverse event
EU	European Union
EUA	emergency use authorization
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition assay
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IM	intramuscular(ly)
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	internet protocol
IPAL	investigational product accountability log
IPM	investigational product manual
IRB	institutional review board

Abbreviation	Term
IRC	internal review committee
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
KDIGO	Kidney Disease: Improving Global Outcomes
LBBB	left bundle branch block
LFT	liver function test
LLOQ	lower limit of quantitation
MDR	medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
mIRV	monovalent influenza modRNA vaccine
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
mRNA	messenger ribonucleic acid
N/A	not applicable
NA	neuraminidase
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
NDCMC	newly diagnosed chronic medical condition
NH	northern hemisphere
NI	noninferiority
NIMP	noninvestigational medicinal product
NYHA	New York Heart Association
Omi	Omicron
PFS	prefilled syringe
PI	principal investigator
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
qIRV	quadrivalent influenza modRNA vaccine
QTcF	QT interval corrected by the Fridericia formula
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Screat	serum creatinine
Scys	serum cystatin C

Abbreviation	Term
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
tIRV	trivalent influenza modRNA vaccine
TIV	trivalent influenza vaccine
UACR	urine albumin/creatinine ratio
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States prescribing information
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee (United States)
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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