A PHASE 1/2 RANDOMIZED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A MODIFIED RNA COVID-19 VACCINE AND A RECOMBINANT INFLUENZA VACCINE ADMINISTERED AS A SINGLE INJECTION IN HEALTHY ADULTS 50 YEARS OF AGE OR OLDER

Study Intervention Number:	PF-08044562
Study Intervention Name:	Combination COVID-19 Vaccine and RIV
US IND Number:	Not Available
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Phase:	1/2
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Evaluate the Safety, Tolerability, and Immunogenicity of a COVID-19 Vaccine and an Influenza Vaccine Given as a Single Injection in Healthy Adults

Document History

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1/2 Randomized Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Modified RNA COVID-19 Vaccine and a Recombinant Influenza Vaccine Administered as a Single Injection in Healthy Adults 50 Years of Age or Older

Brief Title: A Study to Evaluate the Safety, Tolerability, and Immunogenicity of a COVID-19 Vaccine and an Influenza Vaccine Given as a Single Injection in Healthy Adults

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Rationale:

BNT162b2 (Comirnaty®) is a messenger ribonucleic acid (mRNA)-based vaccine that, as of January 2023, has been granted full marketing authorization, conditional marketing authorization, emergency use authorization (EUA), or temporary authorization in a total of more than 184 countries for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The original version of BNT162b2 encodes the ancestral Wuhan-Hu-1 strain spike glycoprotein. In the United States (US), it has been fully licensed for use in individuals 12 years of age and above as of 08 July 2022. All versions of the vaccine encode the SARS-CoV-2 spike protein(s) in nucleoside-modified messenger ribonucleic acid (modRNA) encapsulated in ribonucleic acid lipid nanoparticles (RNA-LNPs), which has demonstrated potent immunogenicity, high vaccine efficacy (VE), and a favorable safety profile in Phase 1, 2, and 3 human trials, as well as in real-world usage. As SARS-CoV-2 continues to circulate, at very high levels, Pfizer/BioNTech are investigating RNA-based COVID-19 vaccines to further protect against COVID-19 caused by emergent and potentially more antigenically diverse variants. BNT162b2 (Omicron [Omi] XBB.1.5), a monovalent vaccine containing mRNA encoding the spike protein of the XBB.1.5 variant, will be used in this study as this is the variant recommended by the Food and Drug Administration (FDA) beginning in fall 2023.

Flublok Quadrivalent (referred to as RIV [recombinant influenza virus]) is a recombinant influenza vaccine, manufactured in a baculovirus expression vector and insect cell culture system, consisting of 4 recombinant influenza hemagglutinin (HA) antigens derived from influenza virus type A, subtypes H1 and H3, and 2 type B virus strains (lineages B/Victoria and B/Yamagata). HA genes from each of the 4 influenza viruses are inserted into a plasmid baculovirus expression vector system (BEVS) and expressed in *Spodoptera frugiperda* insect cells. RIV is indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine, for use in adults 18 years and older.

Annual vaccine programs for SARS-CoV-2 are likely to run concurrently with annual influenza campaigns. In practice, BNT162b2 may be given simultaneously with licensed influenza vaccines.

Combining BNT162b2 with RIV in a single injection would increase the likelihood that persons seeking either vaccination against SARS-CoV-2 or influenza would opt to protect themselves against both pathogens.

This Phase 1/2 study will evaluate the safety, reactogenicity, and immunogenicity of BNT162b2 (Omi XBB.1.5) and RIV administered as a mixture in a single injection.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Safety		
To describe the safety and tolerability of the study interventions	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • Adverse events (AEs) • Serious adverse events (SAEs)	The percentage of participants receiving at least 1 dose of study intervention reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs from vaccination through 4 weeks after vaccination • SAEs from vaccination through 6 months after vaccination

Objectives	Endpoints	Estimands
Immunogenicity		
To describe the immune responses elicited by BNT162b2 (Omi XBB.1.5)/RIV, BNT162b2 (Omi XBB.1.5) + RIV coadministered, and BNT162b2 (Omi XBB.1.5) and RIV administered alone (4 weeks after vaccination)	SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers	In participants complying with the key protocol criteria (evaluable participants): • Geometric mean titers (GMTs) before vaccination and at 4 weeks after vaccination • Geometric mean fold rise (GMFR) from before vaccination to 4 weeks after vaccination • Percentage of participants with seroresponse[a] at 4 weeks after vaccination
	Hemagglutinin inhibition assay (HAI) titers against the seasonal strains recommended by the World Health Organization (WHO) for the northern hemisphere 2023-2024 influenza season	In participants complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 4 weeks after vaccination • GMFRs from before vaccination to 4 weeks after vaccination • The percentages of participants achieving HAI seroconversion[b] at 4 weeks after vaccination • The percentages of participants with HAI titers ≥1:40 before vaccination and at 4 weeks after vaccination

a. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the lower limit of quantitation (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.

Overall Design:

This is a Phase 1/2 single-blind (site- and sponsor-unblinded) study to evaluate the safety, tolerability, and immunogenicity of licensed BNT162b2 (Omi XBB.1.5) and RIV administered together as a single injection (referred to as BNT162b2 [Omi XBB.1.5]/RIV) in healthy adults 50 years of age or older.

The safety, tolerability, and immunogenicity of BNT162b2 (OmiXBB1.5)/RIV administered as a single injection will be compared to BNT162b2 (Omi XBB.1.5) + RIV administered simultaneously as 2 separate injections (coadministered), and to BNT162b2 (Omi XBB.1.5) or RIV when administered alone.

Across Phases 1 and 2, approximately 640 participants in total will be randomized with an equal randomization ratio (1:1:1:1) to each of the following vaccine groups and stratified by age group (50 through 64 years of age and ≥65 years of age):

- **Group 1:** BNT162b2 (Omi XBB.1.5)/ RIV (as a single injection) administered in the left deltoid and placebo administered in the right deltoid
- **Group 2:** BNT162b2 (Omi XBB.1.5) administered in the left deltoid and RIV administered in the right deltoid
- **Group 3:** BNT162b2 (Omi XBB.1.5) administered in the left deltoid and placebo administered in the right deltoid
- **Group 4:** RIV administered in the left deltoid and placebo administered in the right deltoid

During Phase 1, a total of ~20 participants will be enrolled in each vaccine group. Enrollment of participants in each vaccine group will be controlled such that ~10 participants 50 through 64 years of age (sentinel participants, considered Phase 1a) can be vaccinated in each of the groups on the first day. This will be monitored by the sponsor, who will inform sites to pause enrollment once the target has been reached. Vaccination of the remaining ~40 participants (~10 per vaccine group) will commence no sooner than 24 hours after this safety pause. The participants vaccinated after the safety pause will be ≥65 years of age (considered Phase 1b).

Once ~20 participants per vaccine group have been vaccinated in Phase 1, the interactive response technology (IRT) system will block any further randomization, pending a review of at least 72 hours of safety data for all participants by the internal review committee (IRC). The outcome of the safety data review will be documented in a memo, which will be circulated to all sites prior to starting enrollment in Phase 2. In Phase 2, approximately 140 participants 50 years of age or older will be enrolled in each of the 4 vaccine groups. Participants will be stratified by age group, 50 through 64 years of age and ≥65 years of age.

Prespecified local reaction and systemic event data will be collected in an electronic diary (e-diary) during the 7 days, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution), as well as any medications taken during this period to treat any pain symptoms or fever.

Blood samples of approximately 20 mL will be collected from all participants for immunogenicity assessments prior to vaccination and at 4 weeks and 6 months after vaccination.

Following vaccination, AEs will be collected from informed consent signing through Visit 2 (approximately 4 weeks after vaccination), and SAEs will be collected from informed consent signing through Visit 3 (approximately 6 months after vaccination). In addition, AEs occurring up to 48 hours after blood draws will also be collected.

Number of Participants:

Phase 1: Approximately 80 participants will be enrolled.

Phase 2: Approximately 560 participants will be enrolled.

Study Population:

Inclusion Criteria

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

Age and Sex:

1. Male or female participants aged 50 years or older at Visit 1 (Day 1).
    - Refer to the protocol for reproductive criteria for male and female participants.

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

2. Participants who are willing and able to comply with all scheduled visits, the investigational plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.
    - Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.
4. Capable of giving signed informed consent as described in the protocol, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

Exclusion Criteria

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

Medical Conditions:

1. 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.

2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

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

4. Participants with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, temporal arteritis, psoriasis, and/or insulin-dependent diabetes mellitus.

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

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

6. Current heart disease, uncontrolled hypertension, or a prior history of myocarditis or pericarditis.

    - Note: Hypertension that has been controlled a minimum of 12 weeks, stable coronary artery disease, and stable mild valvular disease are not exclusionary.

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

8. Women who are pregnant, plan to become pregnant during the study, or are breastfeeding.

9. Prior history of ischemic stroke or transient ischemic attack.

10. Prior history of Guillain-Barré syndrome (GBS).

11. Participants with a calculated body mass index (BMI) of ≥35.

Prior/Concomitant Therapy:

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

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

13. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies used for the treatment or prevention of COVID-19 or those that are considered immunosuppressive, from 90 days before study intervention administration, or planned receipt throughout the study.

14. Vaccination with any investigational or licensed influenza vaccine within 6 months (180 days) before study intervention administration, or ongoing receipt of chronic antiviral therapy with activity against influenza.

15. Vaccination with any investigational or licensed COVID-19 vaccine within 6 months (180 days) before study intervention administration.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving administration of an investigational product 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:

17. 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.

18. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.

19. Current alcohol abuse or drug addiction that in the opinion of the investigator might interfere with the study conduct or completion.

Study Arms and Duration:

Study Intervention(s)				
Intervention Name	BNT162b2 (Omi XBB.1.5)/RIV	BNT162b2 (Omi XBB.1.5)	RIV	Normal saline placebo
Type	mRNA and recombinant protein vaccine	mRNA vaccine	Recombinant protein vaccine	Placebo
Use	Experimental	Comparator	Comparator	Placebo for blinding
Investigational Medicinal Product (IMP) or Noninvestigational Medicinal Product (NIMP)/Auxiliary Medicinal Product (AxMP)	IMP	IMP	IMP	IMP
Dose Formulation	Suspension for injection and recombinant	Suspension for injection	Solution for injection	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	As detailed in the investigational product manual (IPM)	As detailed in the IPM	As detailed in the IPM	Not applicable (N/A)
Targeted Influenza Strains	As recommended by WHO for cell culture or recombinant-based vaccines (2023-2024 northern hemisphere influenza season)[a]	N/A	As recommended by WHO for cell culture or recombinant-based vaccines (2023-2024 northern hemisphere influenza season)[a]	N/A
Dosage Level(s)	BNT162b2 (Omi XBB.1.5) 30 µg RIV 180 µg	30 µg mRNA	180 µg Recombinant protein	0.5 mL
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor

Study Intervention(s)				
Packaging and Labeling	Study intervention will be generated by mixing the following at the site at the dose-level combinations detailed below: • BNT162b2 (Omi XBB.1.5) • RIV Each vial will be labeled per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement	Study intervention will be provided as either a PFS or a glass/plastic vial as open-label supply	Study intervention will be provided in a plastic vial as open-label supply
Single Reference Safety Document (SRSD)	Combined investigator's brochures (IBs)	IB	Flublok IB	N/A

a. For the 2023-2024 influenza season, Flublok Quadrivalent is formulated to contain 180 µg HA per 0.5-mL dose, with 45 µg HA of each of the following 4 influenza virus strains: A/West Virginia/30/2022 (A/Wisconsin/67/2022 pdm09-like virus) (H1N1), A/Darwin/6/2021 (H3N2), B/Austria/1359417/2021, and B/Phuket/3073/2013.

Statistical Methods:

The sample size is not based on any formal hypothesis test. All statistical analyses will be descriptive. Data from Phase 1 and Phase 2 participants will be combined for the safety and immunogenicity analyses.

The safety primary objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs, and SAEs for each vaccine group. The immunogenicity primary objective will be evaluated descriptively by GMTs and GMFRs of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers and strain-specific HAI titers (for the seasonal strains recommended by WHO), percentages of participants with seroresponse to SARS-CoV-2 Omicron (XBB.1.5), percentages of participants with HAI seroconversion and HAI titers ≥1:40, and the associated 2-sided 95% CIs, for each vaccine group.

Ethical Considerations:

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

- The safety profile of administering BNT162b2 and RIV concomitantly as a single vaccine is not yet fully characterized, so the full extent of risks is unknown.

- Local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain.

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

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

Benefits to individual participants may be:

- Receipt of at least 1 licensed vaccine against COVID-19 or influenza at no cost to the participant, and provision of the immunogenicity results.

- Contributing to research to help others.

1.2. Schema

Phase 1 N = 80			
Group 1 BNT162b2/RIV (1.0 mL) + placebo (0.5 mL)	**Group 2 RIV (0.5 mL) + BNT162b2 (0.3 mL)**	**Group 3 BNT162b2 (0.3 mL) + placebo (0.5 mL)**	**Group 4 RIV (0.5 mL) + placebo (0.5 mL)**
Phase 1a (Participants 50 through 64 years of age)			
Sentinel n = 10	Sentinel n = 10	Sentinel n = 10	Sentinel n = 10
Sponsor Safety Data Review[a] ⬇			
Phase 1b (Participants ≥65 years of age)			
n = 10	n = 10	n = 10	n = 10
IRC[b] ⬇			
Phase 2 N = 560			
Participants ≥50 years of age			
n = 140	n = 140	n = 140	n = 140

a. Progression of the study will occur upon confirmation of an acceptable safety assessment of data accumulated after at least 24 hours and up to 7 days after vaccination.
b. Progression of the study will occur upon confirmation of an acceptable safety assessment of data accumulated after at least 72 hours and up to 7 days after vaccination, once approximately 20 participants in each vaccine group have been vaccinated.

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.

Table 1. Schedule of Activities

Visit Identifier	**1**	**2**	**3**	**Notes**
Visit Window	**Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Day 1 = Day of Vaccination**
Visit Description	**Vaccination**	**4-Week Follow-Up Visit**	**6-Month Follow-Up Visit**	
Visit Type/Location	**Site**	**Site**	**Site**	
Obtain informed consent	X			• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
Assign participant number	X			
Obtain demography and medical history data	X			
Perform clinical assessment, including oral temperature and seated blood pressure	X			Including, if indicated, a physical examination.
Measure height and weight	X			See Section 8.3.1 for additional information.
Collect nonstudy vaccine information, including COVID-19 and influenza vaccine information	X	X	X	See Section 6.9.1 for additional information.
Perform urine pregnancy test on WOCBP	X			See Section 8.3.6 for additional information.

Table 1. Schedule of Activities

Visit Identifier	1	2	3	Notes
Visit Window	**Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Day 1 = Day of Vaccination**
Visit Description	**Vaccination**	**4-Week Follow-Up Visit**	**6-Month Follow-Up Visit**	
Visit Type/Location	**Site**	**Site**	**Site**	
Confirm use of contraceptives (if appropriate)	X	X		See Section 5.3.1 for additional information.
Confirm eligibility	X			See Section 5 for additional information.
Review temporary delay criteria	X			See Section 5.5 for additional information.
Obtain randomization number and study intervention allocation	X			At registration, the participant enrollment number and dose-level allocation are assigned.
Collect blood sample for immunogenicity assessment	~20 mL	~20 mL	~20 mL	• See Section 8.2 for additional information. • For laboratory collection volumes, see the laboratory manual.
Administer study intervention	X			
Postvaccination observation (at least 30 minutes) and assessment of immediate events	X			
Explain participant communication methods (including for reactogenicity e-diary completion), assist the participant with downloading the application, or issue provisioned device, if required	X			See Section 8.3.4 for additional information.
Provide/ensure the participant has a thermometer and measuring device	X			
Review reactogenicity e-diary data (daily review is optimal during the active reactogenicity e-diary period [Days 1 through 7])	◄	►		

Table 1. Schedule of Activities

Visit Identifier	1	2	3	Notes
Visit Window	**Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Day 1 = Day of Vaccination**
Visit Description	**Vaccination**	**4-Week Follow-Up Visit**	**6-Month Follow-Up Visit**	
Visit Type/Location	**Site**	**Site**	**Site**	
Site reviews e-diary data with participant follow-up until ongoing symptom/medication resolution, if applicable		X	X	Review the participant's e-diary data and record assessment in the CRF. Assess compliance, and any medically attended events (including hospitalizations). For symptoms still ongoing, continue to follow up until resolution, and document and record stop dates in the CRF.
Collect reactogenicity e-diary medication use		X		
Collect AEs and SAEs as appropriate	X	X	X	• See Section 8.4 for additional information. • AEs are collected from the completion of informed consent through Visit 2. SAEs are collected from the completion of informed consent through the end of study participation. Additionally, any AEs occurring up to 48 hours after a blood draw must be recorded.
Collect e-diary or assist the participant with deleting the application		X		

2. INTRODUCTION

2.1. Study Rationale

This Phase 1/2 study will evaluate the safety, tolerability, and immunogenicity of licensed BNT162b2 (Omi XBB.1.5) and RIV when administered together in a single injection to healthy adults 50 years of age or older.

Annual vaccine programs for SARS-CoV-2 and influenza are likely to run concurrently. In practice, BNT162b2 may be given simultaneously with licensed influenza vaccines.[1,2]

Combining BNT162b2 with RIV would allow for a single injection and could increase the likelihood that persons seeking either vaccination against SARS-CoV-2 or influenza would opt to protect themselves against both pathogens.

2.2. Background

SARS-CoV-2, a novel β-coronavirus, is a highly transmissible and pathogenic respiratory virus responsible for the ongoing COVID-19 pandemic. Studies of SARS-CoV-2 and SARS-CoV, a closely related coronavirus that caused the 2003 SARS pandemic, 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.

BNT162b2 (Comirnaty®) is an mRNA-based vaccine that, as of January 2023, has been granted full marketing authorization, conditional marketing authorization, EUA, or temporary authorization in a total of more than 184 countries for the prevention of COVID-19 caused by SARS-CoV-2.[5] The original version of BNT162b2 encodes the ancestral Wuhan-Hu-1 strain spike glycoprotein. In the US, it has been fully licensed for use in individuals 12 years of age and above as of 08 July 2022.[6]

With high background rates of population seropositivity, bivalent (original/Omi BA.4/BA.5) mRNA vaccines continued to provide effective protection against Omicron-related COVID-19,[7,8,9,10,11,12] including during periods of early XBB sublineage dominance.[8] Additional bivalent (original/Omi BA.4/BA.5) mRNA doses have been reported to have higher VE against Omicron than the original vaccine,[13] supporting the hypothesis that better strain-matched vaccines improve protection against COVID-19. However, as of May 2023, the descendent sublineages of Omicron XBB (eg, XBB.1.5, XBB.1.16, XBB.1.9) have shown improved transmissibility and reduced susceptibility to neutralization by the bivalent (original/Omi BA.4/BA.5) compared to earlier Omicron strains (eg, BA.1, BA.4, BA.5).[7] Multiple reports have suggested potential waning VE of bivalent BA.4/BA.5 mRNA vaccination against severe illness, as well as less severe endpoints (ie, urgent/emergency care), roughly 2 to 6 months following vaccination.[12,14,15] These data suggest that continual virus evolution toward improved viral fitness, immune escape, and transmission is impacting VE over time.[16] On 12 September 2023, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination for all persons aged ≥6 months with the updated 2023-2024 COVID-19 vaccine including monovalent BNT162b2 (Omi XBB.1.5).[17]

Influenza is a major cause of morbidity and mortality worldwide, occurring in annual seasonal epidemics and occasionally in global pandemics.[18] Symptomatic influenza infection causes a febrile illness with respiratory and systemic symptoms,[19] although it may often be asymptomatic.[20] The risk of complications and hospitalization from influenza are higher in people ≥65 years of age, young children, and people with certain underlying medical conditions. In the US, since 2010 an average of >445,000 hospitalizations per year are related to influenza,[21] while the annual global number of deaths is estimated to range from almost 300,000 to over 600,000.[22]

Influenza viruses are part of the Orthomyxoviridae family and are divided into 4 genera (3 of which are known to infect humans [A, B, and C]).[21,23] Influenza A viruses are further classified into subtypes based upon the membrane glycoproteins, HA and NA.[23] The RNA genome is segmented, which allows for genetic reassortment among influenza A viruses.[23] This genetic instability can result in the phenomenon known as antigenic shift, involving a major change in one (HA) or both (HA + NA) of the surface antigens, which, if efficiently transmissible, can result in a pandemic. More common are multiple point mutations in the genome, leading to more minor changes in the HA and NA, known as antigenic drift.[21] This genetic instability, which can occur in influenza A, B, and C, is what necessitates vaccines that are tailored annually.[21]

Most available influenza vaccines require the culturing of influenza virus in chicken egg cells. The growth process not only introduces opportunity for mutations that are antigenically mismatched to the circulating strain, but the process also requires many months.[24] Flublok is a unique influenza vaccine that harnesses recombinant technology to produce purified HA within 6 to 8 weeks.[24,25]

There is a recommendation in the US for routine annual influenza vaccination for all persons aged ≥6 months who do not have contraindications.[26]

2.2.1. Clinical Overview

2.2.1.1. BNT162b2

Study C4591001 (NCT04368728) was a Phase 1/2/3 trial in ~47,000 participants, designed to generate safety, tolerability, immunogenicity, and efficacy data from a novel RNA-based vaccine candidate. The trial was conducted in a heterogeneous study population: eligible participants ≥12 years of age who are healthy, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants.[27]

Available immunogenicity data from Phase 1 participants showed that BNT162b2 induced a robust IgG-binding response to S1 and a SARS-CoV-2–neutralizing response. Immunogenicity substantially increased following the second dose of vaccine. BNT162b2 induces a strong antigen-specific Th1-skewed CD4+ response and a strong antigen-specific CD8+ response.

In a mid–November 2020 analysis of 36,523 participants randomized 1:1 to vaccine or placebo and who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination schedule, the efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the active vaccine group and 162 COVID-19 cases in the placebo group.[27]

In a subsequent analysis of 927 confirmed symptomatic cases of COVID-19, an efficacy rate of 91.3% was observed for BNT162b2 in preventing such cases occurring between 7 days and 6 months after the second dose.[28] Furthermore, from the same analysis, BNT162b2 was shown to have an efficacy of:

- 100% in preventing severe disease as defined by the CDC.
- 95.3% in preventing severe disease as defined by the FDA.
- 100% in preventing COVID-19 cases in South Africa, where the B.1.351 lineage was prevalent at the time of analysis.

Safety data from approximately 38,000 participants at least 16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose demonstrated a favorable safety profile. Available safety data from all participants enrolled through the 14 November 2020 data cutoff (N = 43,252), which includes late enrollment of additional adolescent and adult participants, were consistent with the safety profile for the approximately 38,000 participants with a median follow-up of 2 months and also did not raise specific safety concerns.[27]

Considering the continuous emergence of variants with cumulative mutations in the spike protein that are resilient to the existing immune response, development of enhanced variant-specific vaccines that generate improved immune responses against the variants remains imperative, to better protect individuals against COVID-19.

WHO issued its statement on the antigen composition of COVID-19 vaccines on 18 May 2023 recommending use of a monovalent XBB.1 descendent lineage, such as XBB.1.5, as the vaccine antigen.[7] The EMA released similar guidance on 06 June 2023 recommending that a monovalent vaccine targeting the XBB.1 descendent lineages be administered beginning in autumn 2023.[29] On 11 September 2023, the FDA approved authorization of a monovalent vaccine targeting the XBB.1.5 Omicron subvariant.[30,31]

2.2.1.2. RIV

RIV was studied in a Phase 3 multicenter, randomized, double-blind controlled trial in adults 65 years of age and older during the 2006-2007 influenza season where participants were randomized to RIV or a licensed trivalent influenza vaccine. The frequency and severity of injection site reaction and systemic events after immunization were similar in both groups. RIV was found to be both safe and well tolerated.[32,33]

Trivalent RIV was studied in a randomized trial study of 4648 individuals 18 to 55 years of age during the 2007-2008 influenza season. RIV was well tolerated, immunogenic, and protective against culture-confirmed influenza.[33,34]

Trivalent RIV was studied in a Phase 3 observer-blind study in heathy adults 50 to 64 years of age during the 2007-2008 influenza season and was found to be both safe and immunogenic.[33,35]

Quadrivalent RIV was studied in an observer-blind, randomized, active-controlled, Phase 3 study of 1350 individuals aged 18 to 49 years during the 2014-2015 influenza season. RIV was compared directly with a standard-dose, egg-grown, quadrivalent-inactivated influenza vaccine for immunogenicity and safety. Quadrivalent RIV showed comparable safety, tolerability, and immunogenicity to inactivated quadrivalent influenza vaccine.[36]

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162b2 (Omi XBB.1.5)/RIV may be found in the combined IBs, which is the SRSD for this study. The SRSD for BNT162b2 (Omi XBB.1.5) and RIV is the Comirnaty® IB and Flublok Quadrivalent IB, respectively. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): BNT162b2 (Omi XBB.1.5)/RIV administered together as a single injection or BNT162b2 (Omi XBB.1.5) and RIV administered simultaneously		
Allergic reactions/anaphylaxis may occur.	Allergic reactions have been observed with an unknown frequency.	Sites will have appropriate medication and supportive measures for management of an acute hypersensitivity reaction.
Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines,[37] as well as the COVID-19 vaccine BNT162b2. 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.[27] The most common adverse reactions seen in a placebo-controlled safety and efficacy trial of RIV were local injection site pain, muscle aches, headache, and fatigue or lack of energy.[34] Slightly increased reactogenicity has been shown when a COVID-19 booster is coadministered with an influenza vaccine.[38]	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time after each 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.
The safety profile of a novel vaccine is not yet fully characterized.	BNT162b2 (Omi XBB1.5)/RIV is a novel combination; however, the individual active components from which it is made have been shown to have a positive benefit/risk profile.	AE and SAE reports will be collected from the signing of the ICD through 4 weeks and 6 months, respectively, after vaccination. All participants will be observed for at least 30 minutes after vaccination.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): BNT162b2 (Omi XBB.1.5)		
This vaccine has the same modRNA platform and LNP formulation as the original BNT162b2; therefore, the safety profile is expected to be similar to that of BNT162b2, ie, local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain. Other key risks identified for BNT162b2 are lymphadenopathy; hypersensitivity reactions, such as rash, pruritus, urticaria, angioedema, and anaphylaxis; and myocarditis and pericarditis.	These are common adverse reactions seen with other vaccines as well as the COVID-19 vaccine. 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.[27] Anaphylaxis: Frequency not known. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with modRNA SARS-CoV-2 vaccines after authorization. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients. 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.	Local reactions and systemic events will be recorded using a reactogenicity e-diary to monitor local reactions and systemic events in real time after vaccination. AE and SAE reports will be collected from the signing of the ICD through 4 weeks and 6 months, respectively, after vaccination. Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.10.5.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): RIV (Flublok)		
Local and systemic reactions to the vaccines may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) following vaccination.	These are common reactions seen with other vaccines as well as RIV.[33,37] Anaphylaxis: Frequency not known. GBS: The 1976 swine influenza vaccine was associated with an increased frequency of GBS. Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated. If GBS has occurred within 6 weeks after receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of the potential benefits and risks.[33] Altered immunocompetence: If RIV is administered to immunocompromised individuals, including persons receiving immunosuppressive therapy, the immune response may be diminished.[33] Limitations of vaccine effectiveness: Vaccination with RIV may not protect all vaccine recipients.[33]	AE and SAE reports will be collected from the signing of the ICD through 4 weeks and 6 months, respectively, after vaccination. All study participants will be observed for at least 30 minutes after vaccination. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Immunocompromised individuals and individuals receiving immunosuppressive therapies will be excluded from Phase 1 and 2 of this study.
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 an efficacious or potentially efficacious COVID-19 vaccine.
- Receipt of an efficacious or potentially efficacious influenza vaccine.
- Receipt of both a COVID-19 vaccine and an influenza vaccine.
- Contributing to research to help others.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with BNT162b2 (Omi XBB.1.5)/RIV are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Safety		
To describe the safety and tolerability of the study interventions	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	The percentage of participants receiving at least 1 dose of study intervention reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs from vaccination through 4 weeks after vaccination • SAEs from vaccination through 6 months after vaccination
Immunogenicity		
To describe the immune responses elicited by BNT162b2 (Omi XBB.1.5)/RIV, BNT162b2 (Omi XBB.1.5) + RIV coadministered, and BNT162b2 (Omi XBB.1.5) and RIV administered alone (4 weeks after vaccination)	SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers	In participants complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 4 weeks after vaccination • GMFR from before vaccination to 4 weeks after vaccination • Percentage of participants with seroresponse[a] at 4 weeks after vaccination

Objectives	Endpoints	Estimands
	HAI titers against the seasonal strains recommended by WHO for the northern hemisphere 2023-2024 influenza season	In participants complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 4 weeks after vaccination • GMFRs from before vaccination to 4 weeks after vaccination • The percentages of participants achieving HAI seroconversion[b] at 4 weeks after vaccination • The percentages of participants with HAI titers ≥1:40 before vaccination and at 4 weeks after vaccination
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by BNT162b2 (Omi XBB.1.5)/RIV, BNT162b2 (Omi XBB.1.5) + RIV coadministered, and BNT162b2 (Omi XBB.1.5) and RIV administered alone (6 months after vaccination)	SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers	In participants complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 6 months after vaccination • GMFR from before vaccination to 6 months after vaccination • Percentage of participants with seroresponse[a] at 6 months after vaccination
	HAI titers against the seasonal strains recommended by WHO for the northern hemisphere 2023-2024 influenza season	In participants complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 6 months after vaccination • GMFRs from before vaccination to 6 months after vaccination • The percentages of participants achieving HAI seroconversion[b] at 6 months after vaccination • The percentages of participants with HAI titers ≥1:40 before vaccination and at 6 months after vaccination
To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern)	SARS-CoV-2–neutralizing titers and/or HAI titers for variants (under monitoring, of interest, and/or of concern) not already specified	

Objectives	Endpoints	Estimands
To descriptively compare the immune responses between vaccine groups	SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers and HAI titers for the seasonal strains recommended by WHO	GMRs and differences in percentage of participants with seroresponse or seroconversion between vaccine groups
To describe the immune response elicited by RIV using virus microneutralization assays	HAI titers against the seasonal strains recommended by WHO for the northern hemisphere 2023-2024 influenza season	

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 single-blind (site- and sponsor-unblinded) study to evaluate the safety, tolerability, and immunogenicity of licensed BNT162b2 (Omi XBB.1.5) and RIV administered together as a single injection (referred to as BNT162b2 [Omi XBB.1.5]/RIV) in healthy adults 50 years of age or older.

The safety, tolerability, and immunogenicity of BNT162b2 (OmiXBB1.5)/RIV administered as a single injection will be compared to BNT162b2 (Omi XBB.1.5) and RIV administered simultaneously as 2 separate injections (coadministered), and to BNT162b2 (Omi XBB.1.5) or RIV when administered alone.

Across Phases 1 and 2, approximately 640 participants in total will be randomized with an equal randomization ratio (1:1:1:1) to each of the following vaccine groups and stratified by age group (50 through 64 years of age and ≥65 years of age):

- **Group 1:** BNT162b2 (Omi XBB.1.5)/RIV (as a single injection) administered in the left deltoid and placebo administered in the right deltoid
- **Group 2:** BNT162b2 (Omi XBB.1.5) administered in the left deltoid and RIV administered in the right deltoid
- **Group 3:** BNT162b2 (Omi XBB.1.5) administered in the left deltoid and placebo administered in the right deltoid
- **Group 4:** RIV administered in the left deltoid and placebo administered in the right deltoid

During Phase 1, a total of ~20 participants will be enrolled in each vaccine group. Enrollment of participants in each vaccine group will be controlled such that ~10 participants 50 through 64 years of age (sentinel participants, considered Phase 1a) can be vaccinated in each of the groups on the first day. This will be monitored by the sponsor, who will inform sites to pause enrollment once the target has been reached. Vaccination of the remaining ~40 participants (~10 per vaccine group) will commence no sooner than 24 hours after this safety pause. The participants vaccinated after the safety pause will be ≥65 years of age (considered Phase 1b).

Once ~20 participants per vaccine group have been vaccinated in Phase 1, the IRT system will block any further randomization, pending a review of at least 72 hours of safety data for all participants by the IRC. The outcome of the safety data review will be documented in a memo, which will be circulated to all sites prior to starting enrollment in Phase 2. In Phase 2, 140 participants 50 years of age or older will be enrolled in each of the 4 vaccine groups (Table 2). Participants will be stratified by age group, 50 through 64 years of age and ≥65 years of age.

Table 2. Phase 1/2 Vaccine Group Summary

Vaccine Group Number	Vaccine Group Description	Phase 1[a] (Number of Participants per Vaccine Group)	Phase 2[b] (Number of Participants per Vaccine Group)
1	BNT162b2 (Omi XBB.1.5)/RIV and placebo	20	140
2	BNT162b2 (Omi XBB.1.5) and RIV	20	140
3	BNT162b2 (Omi XBB.1.5) and placebo	20	140
4	RIV and placebo	20	140

a. Phase 1a participants will be 50 through 64 years of age at Visit 1 (Day 1). Phase 1b participants will be ≥65 years of age at Visit 1 (Day 1).
b. Phase 2 participants will be 50 years of age or older at Visit 1 (Day 1).

Prespecified local reaction and systemic event data will be collected in an e-diary during the 7 days, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution), as well as any medication taken during this period to treat any pain symptoms or fever.

Blood samples of approximately 20 mL will be collected from all participants for immunogenicity assessments prior to vaccination and at 4 weeks and 6 months after vaccination.

Following vaccination, AEs will be collected from informed consent signing through Visit 2 (approximately 4 weeks after vaccination), and SAEs will be collected from informed consent signing through Visit 3 (approximately 6 months after vaccination). In addition, AEs occurring up to 48 hours after blood draws will also be collected.

4.2. Scientific Rationale for Study Design

The overall scientific rationale for the study design is presented in Section 2.1.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for the RIV used in this study, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. The use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

4.3.1. Monovalent BNT162b2 (Omi XBB.1.5)

The 30-µg dose level of BNT162b2 was shown to be effective and is licensed for use in the US.[39]

4.3.2. RIV

The 180-µg dose level of RIV was shown to be effective and is licensed for use in the US.[33]

4.3.3. BNT162b2 (Omi XBB.1.5)/RIV

This will be a combination of BNT162b2 (Omi XBB.1.5) and RIV using the dose levels detailed in Section 4.3.1 and Section 4.3.2.

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 the last visit of the study.

5. STUDY POPULATION

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

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

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants aged 50 years or older 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, the investigational plan, laboratory tests, lifestyle considerations, and other study procedures.

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

    - Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. 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.

2. Known infection with HIV, HCV, or HBV.

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

4. Participants with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, temporal arteritis, psoriasis, and/or insulin-dependent diabetes mellitus.

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

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

6. Current heart disease, uncontrolled hypertension, or a prior history of myocarditis or pericarditis.

    - Note: Hypertension that has been controlled a minimum of 12 weeks, stable coronary artery disease, and stable mild valvular disease are not exclusionary.

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

8. Women who are pregnant, plan to become pregnant during the study, or are breastfeeding.

9. Prior history of ischemic stroke or transient ischemic attack.

10. Prior history of GBS.

11. Participants with a calculated BMI of ≥35.

Prior/Concomitant Therapy:

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

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

13. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies used for the treatment or prevention of COVID-19 or those that are considered immunosuppressive, from 90 days before study intervention administration, or planned receipt throughout the study.

14. Vaccination with any investigational or licensed influenza vaccine within 6 months (180 days) before study intervention administration, or ongoing receipt of chronic antiviral therapy with activity against influenza.

15. Vaccination with any investigational or licensed COVID-19 vaccine within 6 months (180 days) before study intervention administration.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving administration of an investigational product 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:

17. 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.

18. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.

19. Current alcohol abuse or drug addiction that in the opinion of the investigator might interfere with the study conduct or completion.

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. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

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

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

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen 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 once the conditions have resolved and the participant is otherwise eligible. Participants meeting these criteria at Visit 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

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

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

- Receipt of any nonstudy vaccine within 28 days before study intervention administration at Visit 1.

- Anticipated receipt of any nonstudy vaccine within 28 days after study intervention administration at Visit 1.

- Receipt of short-term (<14 days) systemic corticosteroids 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: 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 investigational and medical devices, and other interventions (eg, surgical and behavioral), intended to be administered to the study participants during the study conduct.

6.1. Study Intervention(s) Administered

Participants will be enrolled and randomized to each of the following vaccine groups:

- **Group 1:** BNT162b2 (Omi XBB.1.5)/RIV (as a single injection) administered in the left deltoid and placebo administered in the right deltoid

- **Group 2:** BNT162b2 (Omi XBB.1.5) administered in the left deltoid and RIV administered in the right deltoid

- **Group 3:** BNT162b2 (Omi XBB.1.5) administered in the left deltoid and placebo administered in the right deltoid

- **Group 4:** RIV administered in the left deltoid and placebo administered in the right deltoid

Study Intervention(s)				
Intervention Name	BNT162b2 (Omi XBB.1.5)/RIV	BNT162b2 (Omi XBB.1.5)	RIV	Normal saline placebo
Type	mRNA and recombinant protein vaccine	mRNA vaccine	Recombinant protein vaccine	Placebo
Use	Experimental	Comparator	Comparator	Placebo for blinding
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP
Dose Formulation	Suspension for injection and Recombinant	Suspension for injection	Solution for injection	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	As detailed in the IPM	As detailed in the IPM	As detailed in the IPM	N/A
Targeted Influenza Strains	As recommended by WHO for cell culture or recombinant-based vaccines (2023-2024 northern hemisphere influenza season)[a]	N/A	As recommended by WHO for cell culture or recombinant-based vaccines (2023-2024 northern hemisphere influenza season)[a]	N/A
Dosage Level(s)	BNT162b2 (Omi XBB.1.5) 30 µg RIV 180 µg	30 µg mRNA	180 µg Recombinant protein	0.5 mL
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor

Study Intervention(s)				
Packaging and Labeling	Study intervention will be generated by mixing the following at the site at the dose-level combinations detailed below: • BNT162b2 (Omi XBB.1.5) • RIV Each vial will be labeled per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement	Study intervention will be provided as either a PFS or a glass/plastic vial as open-label supply	Study intervention will be provided in a plastic vial as open-label supply
SRSD	Combined IBs	IB	Flublok IB	N/A

a. For the 2023-2024 influenza season, Flublok Quadrivalent is formulated to contain 180 µg HA per 0.5-mL dose, with 45 µg HA of each of the following 4 influenza virus strains: A/West Virginia/30/2022 (A/Wisconsin/67/2022 pdm09-like virus) (H1N1), A/Darwin/6/2021 (H3N2), B/Austria/1359417/2021, and B/Phuket/3073/2013.

Study Arm(s)				
Group	1	2	3	4
Arm Title	BNT162b2 (Omi XBB.1.5)/RIV + normal saline placebo	BNT162b2 (Omi XBB.1.5) + RIV	BNT162b2 (Omi XBB.1.5) + normal saline placebo	RIV + normal saline placebo
Arm Description	Participants will receive a single injection combination of BNT162b2 (Omi XBB.1.5) (30 µg) and RIV (180 µg) administered in the left deltoid and normal saline placebo administered in the right deltoid at Visit 1 (Day 1)	Participants will receive BNT162b2 (Omi XBB.1.5) (30 µg) administered in the left deltoid and RIV (180 µg) administered in the right deltoid at Visit 1 (Day 1)	Participants will receive BNT162b2 (Omi XBB.1.5) (30 µg) administered in the left deltoid and normal saline placebo administered in the right deltoid at Visit 1 (Day 1)	Participants will receive RIV (180 µg) administered in the left deltoid and normal saline placebo administered in the right deltoid

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 will receive 2 injections at Visit 1 as randomized in accordance with the SoA. Study intervention should be administered intramuscularly into the deltoid muscle of the appropriate arm as detailed in Table 3, and in such a way as to ensure that the participants remain blinded.

Table 3. Anatomical Location for Study Intervention Administration

Vaccine Group Number	Left Deltoid[a]	Right Deltoid[a]
1	BNT162b2 (Omi XBB.1.5)/RIV	Placebo
2	BNT162b2 (Omi XBB.1.5)	RIV
3	BNT162b2 (Omi XBB.1.5)	Placebo
4	RIV	Placebo

a. Study intervention will be administered in contralateral arms. Local reactions will be assessed at the injection site on both the left and right deltoids.

6.1.2. Medical Devices

RIV and normal saline placebo may be provided as a PFS, in which case the PFS should be considered a medical device.

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

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

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

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

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

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

6.2.1. Preparation and Dispensing

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

6.3. Assignment to Study Intervention

Allocation (randomization) of participants to study arms will proceed through the use of an IRT system (IWR). 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 study intervention.* The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. Confirmation report must be stored in the site's files.

* Do not randomize until eligibility is confirmed and the participant is present.

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 a single-blind study.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be unblinded to participants' assigned study intervention.

6.4.3. Blinding of the Sponsor

Sponsor staff will be unblinded to participants' assigned study intervention.

6.4.4. Breaking the Blind

Not applicable.

6.5. Study Intervention Compliance

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

6.6. Dose Modification

Not applicable.

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

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

6.8. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs as medically appropriate and 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 in the CRF.

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

6.9. Prior and Concomitant Therapy

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

- Receipt of any COVID-19 vaccine from 12 months prior to enrollment until the last visit (Visit 3).

- Receipt of licensed or investigational influenza vaccine from 12 months prior to enrollment until the last visit (Visit 3).

- Any vaccinations received from 28 days prior to Visit 1 until the last visit (Visit 3).

- Details of any concomitant medication taken to treat fever or pain (solicited reactogenicity symptoms) as reported in the e-diary will be collected.

6.9.1. Prohibited During the Study

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

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 14 days before and 14 days after study vaccination at Visit 1.

- Receipt of any other (nonstudy) coronavirus vaccine from enrollment throughout the entire study is prohibited.

- Receipt of any other (nonstudy) seasonal influenza vaccine from enrollment throughout the entire study is prohibited.

- Receipt of chronic medications with known systemic immunosuppressant effects, or radiotherapy, within 60 days before enrollment through conclusion of the study is prohibited.

- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment through 28 days after administration of the study intervention.

- Planned receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies, from 90 days before study intervention administration through conclusion of the study, is prohibited.

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

6.9.2. Permitted During the Study

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

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

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (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 for any further evaluations that need to be completed.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Reactogenicity event;
- AEs;
- Participant request;
- Investigator request;
- Select protocol deviations (eg, receipt of a COVID-19 and influenza vaccine at any time during this study).

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

Age will be collected to critically evaluate the immune response and safety profile by age.

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

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

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

The total blood sampling volume for individual participants in this study is approximately 60 mL The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, 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.

8.2. Efficacy and/or Immunogenicity Assessments

Samples will be collected at the time points specified in the SoA from all participants and the following assays will be performed:

- SARS-CoV-2 neutralization assays (Omi XBB.1.5).
- HAI titers (from HAI based on cell-derived virus) for the seasonal strains (2×A, 2×B) recommended by WHO.

To describe the immune response to emerging variants of SARS-CoV-2 and/or influenza, additional assay may be run on an exploratory basis.

Virus microneutralization assays may be run on all or a subset of samples on an exploratory basis as detailed in the SAP.

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

The N-binding antibody test will 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 during study participation may be performed if assays are available.

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, pulse rate, and seated blood pressure 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

All participants will be required to complete a reactogenicity e-diary after vaccination given at Visit 1, through an application installed on a provisioned device or on the participant's own personal device. All participants will be asked to monitor and record local reactions, systemic events, and use of any medication for solicited pain symptoms or fever for 7 days, or longer for ongoing symptoms, from the day of administration of the study intervention given at Visit 1. The reactogenicity e-diary allows recording of these assessments each day, thus providing the accurate representation of the participant's experience. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. Generally, these data do not need to be reported by the investigator in the CRF as AEs. However, if a participant has a serious adverse event reported in the e-diary, the event(s) should be recorded on the CRF, regardless of whether the investigator considers the event(s) to be related. If a participant missed reporting an event in the e-diary and reports it to the study site instead, the event should also be recorded on the CRF.

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.

The investigator or designee must obtain stop dates from the participant for any symptoms ongoing on the last day from Day 7 onwards and follow up daily until resolution. The stop dates should be documented in the source documents and the information entered in the CRF.

8.3.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[37]

8.3.4.2. Local Reactions

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

If a local reaction persists beyond the end of the 7-day e-diary collection period following vaccination, the participant will be requested to report that information and/or any new reactogenicity reactions that develop to the investigator or the study staff. The investigator will enter this additional information in the CRF.

Participants will be provided with a measuring device. Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 4. 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 4.

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

Table 4. 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

Table 4. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
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

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

If a systemic event persists beyond the end of the 7-day e-diary collection period following vaccination, the participant will be requested to report that information and/or any new reactogenicity events that develop to the investigator or the study staff. The investigator will enter this additional information in the CRF. If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor. A Grade 4 systemic event will be collected on the CRF.

Table 5. Systemic Event Grading Scale

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

Table 5. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
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 thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary daily for 7 days or longer following vaccination (where Day 1 is the day of vaccination). It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 6 during analysis.

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

Table 6. Scale for Fever

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

8.3.4.5. Antipyretic Medication

The use of antipyretic medications to treat pain symptoms or fever associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the 7-day reporting period or longer for ongoing symptoms.

8.3.5. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2 or 30 days after the administration of the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded so 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 for the impacted vaccine group.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity 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 the administration of study intervention. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule. Once the IRC have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

Stopping Rule Criteria for Each Vaccine Group:

- If any vaccinated participant develops an SAE that is assessed by the investigator as possibly related to the study intervention, or for which there is no alternative, plausible, attributable cause.
- If any participant develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.3.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

- If any participant develops a fever >40°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.3.4.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
- If any vaccinated participant develops confirmed myocarditis or pericarditis.
- If any vaccinated participant dies.
- If any vaccinated participant experiences a Grade 4 unsolicited AE, or SAE of any severity, assessed as related to the study intervention by the investigator.
- If any 2 participants vaccinated participants develop the same or similar Grade 3 or higher unsolicited AE, other than myocarditis/pericarditis, assessed as related to study intervention by the investigator. Note that the solicited local reactions, systemic events, and fever specified in Section 8.3.4, reported within 7 days from the day of administration of the study intervention, irrespective of whether they are recorded in the e-diary or as AEs, are excluded from this stopping rule.

8.3.6. 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.

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

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

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

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

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

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 2. At Visit 3 (approximately 6 months after vaccination), the participant will be asked about AESIs since Visit 1.

Additionally, any AEs occurring up to 48 hours after any subsequent blood draws must be recorded in the CRF.

SAEs will be collected from the time the participant provides informed consent through the duration of the study (Visit 3, approximately 6 months after vaccination).

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

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

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

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

If a participant permanently discontinues or temporarily discontinues from the study because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form or 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 using the Vaccine SAE Report Form or 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 on the Vaccine SAE Report Form/PSSA immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

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

- A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then inseminates his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety using the Vaccine SAE Report Form and an EDP Supplemental Form or 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 study intervention.

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

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

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form or 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 using the Vaccine SAE Report Form or 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

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

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

Not applicable.

8.4.8. Adverse Events of Special Interest

The following events are protocol-specified AESIs:

- Confirmed COVID-19 diagnosis (clinical signs/symptoms and positive SARS-CoV-2 NAAT or antigen test) after Visit 1 through the end of the study.
- Confirmed diagnosis of myocarditis or pericarditis occurring after vaccination. See Section 8.10.5.
- Potential menstrual cycle disturbances. See Section 8.10.6.
- GBS.
- Neuritis, including Bell's palsy.
- Vasculitis.

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 Section 8.4.1 through Section 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using Vaccine SAE Report Form or 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 7.

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 10.7.4 for instructions for documenting and reporting medical device deficiencies.

8.4.9.2. Follow-Up of Medical Device Deficiencies

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

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

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

8.4.9.3. Regulatory Reporting Requirements for Device Deficiencies

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

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

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

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

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

8.4.10. Vaccination Errors

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

Vaccination errors are recorded and reported as follows:

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

Vaccination errors include:

- Vaccination errors involving participant exposure to the study intervention;

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

- The administration of expired study intervention;

- 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.

    - The administration of the prepared combined vaccine after more than 4 hours of storage at 25°C.

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

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

Not applicable.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Refer to Section 8.2.

8.9. Health Economics

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

8.10. Study Procedures

8.10.1. Visit 1 – Vaccination (Day 1)

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

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

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including age in years, sex, race, and ethnicity).
- Obtain medical history and any other medical history of clinical significance.

- On the day of and prior to study intervention administration, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record findings on the medical history CRF.

- Measure the participant's height and weight.

- On the day of and prior to study intervention administration, measure the participant's oral temperature and seated blood pressure.

- Record nonstudy vaccinations and prior receipt of any licensed or investigational COVID-19 or influenza vaccine as described in Section 6.9.

- On the day of and prior to study intervention administration, perform a urine pregnancy test on WOCBP as described in Section 8.3.6.

- If applicable, discuss contraceptive use as described in Section 10.4.4.

- On the day of and prior to study intervention administration, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- On the day of and prior to study intervention administration, ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- On the day of and prior to study intervention administration, obtain the participant's randomization number and study intervention allocation using the IRT system.

- On the day of and prior to study intervention administration, collect a blood sample (approximately 20 mL), before administration of study intervention, for immunogenicity assessment.

- Site staff member(s) will dispense/administer 2 injections (1 in each arm) into the deltoid muscle of the prescribed arm based on the study intervention allocation as detailed in Table 3. Please refer to the IPM for further instruction on this process.

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

- Explain the e-diary technologies available for this study (see Section 8.3.4), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.

- Provide instructions on reactogenicity e diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7 or longer until any symptoms that are ongoing are resolved, with Day 1 being the day of vaccination.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures; provide instructions on their use.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
  - Record AEs as described in Section 10.3.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.5).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and a dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online and records the assessment in the CRF following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.10.2. Visit 2 – 4-Week Follow-Up Visit (After Vaccination) – 28 to 35 Days After Visit 1

- Record AEs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 6.9.
- If applicable, discuss contraceptive use as described in Section 10.4.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Review the participant's reactogenicity e-diary data and record assessment in the CRF. Assess compliance, record any medically attended events (including hospitalizations), and collect stop dates for any symptoms/medications ongoing on the last day of the e-diary collection period in the CRF. For symptoms still ongoing, continue to follow up until resolution, and document and record stop dates in the CRF.
- Record reactogenicity medication used as described in Section 8.3.4.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.4.

8.10.3. Visit 3 – 6-Month Follow-Up Visit (After Vaccination) – 175 to 189 Days After Visit 1

- Record SAEs and AESIs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 6.9.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.4.

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

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

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

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

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be followed daily until resolution.

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

- Measure oral temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.3.4.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.3.4.3.
- Assess for other findings associated with the reaction and record these on the CRF if appropriate.

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

8.10.5. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports the following within 28 days after the study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis:

- Acute chest pain,
- Shortness of breath,
- Palpitations, or
- Any other symptom(s) that might be indicative of myocarditis or pericarditis.

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

- ECG and
- Measurement of the troponin level.

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

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study.
- Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF. Any diagnosis made (myocarditis, pericarditis, or other) should be recorded as an SAE. Refer also to Section 8.4.8.

8.10.6. Additional Procedures for Monitoring of Potential Menstrual Cycle Disturbances

Any female study participant who reports any symptoms that may indicate a disturbance of their normal menstrual cycle (including, but not exclusively, 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.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

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

9.1.1. Estimands

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

The safety primary objective evaluations are based on the safety population. In general, completely missing reactogenicity data (ie, all 7 days of collection were missing) will not be imputed. For partially missed reactogenicity data (eg, 1-6 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 objective are based on the evaluable immunogenicity population (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. 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 at least 1 dose of the study intervention.

Participant Analysis Set	Description
Evaluable immunogenicity	All eligible assigned participants who receive the study intervention to which they are assigned, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All assigned participants who receive the study intervention and have 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

Other than IRC review of early Phase 1 safety data before initiation of Phase 2 enrollment, data from Phase 1 and Phase 2 participants will be combined for the safety and immunogenicity analyses.

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

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

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 were 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).[40] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.

9.3.1.2. Analysis for Continuous Data

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

9.3.1.2.1. Geometric Means

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

9.3.1.2.2. Geometric Mean Ratios

Model-Based GMR:

The GMR and associated 95% CI will be calculated by exponentiating the difference in LS means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model that includes terms for baseline assay results (log scale), age, and comparison group.

Unadjusted GMR:

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

9.3.1.2.3. 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.

9.3.1.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with 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. 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 severity and cumulatively across severity levels. 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 4 weeks and SAEs from vaccination through 6 months after vaccination will be provided for each vaccine group.
Immunogenicity	• GMTs and 2-sided 95% CIs of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers and strain-specific HAI titers (for the seasonal strains recommended by WHO) before vaccination and at 4 weeks after vaccination will be provided for each vaccine group. Statistical methods are described in Section 9.3.1.2.1. • GMFRs of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers and strain-specific HAI titers (for the seasonal strains recommended by WHO) from before vaccination to 4 weeks after study vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group. Statistical methods are described in Section 9.3.1.2.3. • The percentages of participants with seroresponse to SARS-CoV-2 Omicron (XBB.1.5) at 4 weeks after vaccination, the percentages of participants with HAI seroconversion at 4 weeks after vaccination, and percentages of participants with HAI titers ≥1:40 before vaccination and at 4 weeks after vaccination and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group.

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

Not applicable.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

Immunogenicity	• GMTs and 2-sided 95% CIs of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers and strain-specific HAI titers (for the seasonal strains recommended by WHO) before vaccination and at 6 months after vaccination will be provided for each vaccine group. Statistical methods are described in Section 9.3.1.2.1. • GMFRs of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers and strain-specific HAI titers (for the seasonal strains recommended by WHO) from before vaccination to 6 months after study vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group. Statistical methods are described in Section 9.3.1.2.3. • The percentages of participants with seroresponse to SARS-CoV-2 Omicron (XBB.1.5) at 6 months after vaccination, the percentages of participants with HAI seroconversion at 6 months after vaccination, and percentages of participants with HAI titers ≥1:40 before vaccination and at 6 months after vaccination and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group.
Immune response to emerging variants	• For SARS-CoV-2-neutralizing titers and/or HAI titers for emerging variants (under monitoring, of interest, and/or of concern), GMTs, GMFRs, percentages of participants with seroresponse, and percentages of participants with seroconversion or HAI titers ≥1:40 at the specific time point, along with the associated 95% CIs, will be summarized in the same way as for the immunogenicity primary endpoints described above. This analysis may be conducted in a selected subset of participants.
Descriptive comparison of immune response	• GMRs and the differences in percentages of participants with seroresponse to SARS-CoV-2 Omicron (XBB.1.5) and with HAI seroconversion between certain groups of interest will be calculated along with the associated 2-sided 95% CIs.
HAI titers by virus microneutralization assay	• For HAI titers measured by virus microneutralization assays, GMTs, GMFRs, and percentages of participants with seroconversion or HAI titers ≥1:40 at the specific time point, along with the associated 95% CIs, will be summarized in the same way as for the immunogenicity primary endpoints described above. This analysis may be conducted in a selected subset of participants.

9.4. Interim Analyses

No 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:

- Safety and immunogenicity data through 4 weeks 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 7 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 1%, with approximately 160 participants in a vaccine group, there is 80% probability of observing at least 1 AE.

Table 7. Probability of Observing at Least 1 AE, by Assumed True Event Rate

Assumed True Event Rate of an AE	N=20	N=80	N=160	N=640
0.1%	0.02	0.08	0.15	0.47
0.5%	0.10	0.33	0.55	0.96
1%	0.18	0.55	0.80	>0.99
2%	0.33	0.80	0.96	>0.99
3%	0.46	0.91	0.99	>0.99
4%	0.56	0.96	>0.99	>0.99
5%	0.64	0.98	>0.99	>0.99

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

10.1.3.1. Electronic Consent

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

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

The IRC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities and investigators, as appropriate.

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.

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

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

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

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

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

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

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

10.1.8. Source Documents

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

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

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

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

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

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

10.1.9. Use of Medical Records

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

Due to the potential for a participant to be re-identified 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 identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

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

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

10.1.10. Study and Site Start and Closure

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

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

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

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

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

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

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

10.1.11. Publication Policy

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

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

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

study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

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

10.1.12. Sponsor's Medically Qualified Individual

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs using the Vaccine SAE Report Form or 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 Vaccine SAE Report Form/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 Vaccine SAE Report Form/PSSA for reporting of SAE information.

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

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form or via PSSA.

** **EDB** is reported to Pfizer Safety using the Vaccine SAE Report Form or 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 using the Vaccine SAE Report Form or 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 in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

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

Assessment of Causality

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

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eg, eSAE or PSSA). • If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data. • 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 one of the preferred methods to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE 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.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

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

  - Agree to use a male condom, 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 who is not currently pregnant.

  OR

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

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

  OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

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

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.

8. Sexual abstinence

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

Other Effective Methods

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

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, 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 the 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/1.73m²)

2021 CKD-EPI Screat Only	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤.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	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

Inker LA et al. N Engl J Med. 2021;385(19):1737-49.[41]

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 the screening, baseline, and postbaseline visits. Site calculations of kidney function can be performed manually, using the age-appropriate formulae (see Section 10.6.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

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

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

10.6.4. 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 both pediatric and adult participants.

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

KDIGO albuminuria (A) criteria	**A1**	**A2**	**A3**
Albumin-to-creatinine ratio (ACR)	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

10.7. Appendix 7: 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).

10.7.1. 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.

10.7.2. 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.

10.7.3. 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.

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

Device Deficiency Recording
• When a device deficiency 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 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 investigator will notify the sponsor study team by contact method, eg, telephone, email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency. • The sponsor study team will capture the required information on the Medical Device Complaint form along with any associated AE (either serious or nonserious) when applicable and send to the appropriate product quality complaint group. • If the investigator 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 investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. All relevant details related to the role of the device

in regard to the SAE must be included in the Vaccine SAE Report Form as outlined in Sections 8.4.1.1 and 8.4.1.2.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

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

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency

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

10.8. Appendix 8: 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
ACR	albumin-to-creatinine ratio
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BEVS	baculovirus expression vector system
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BNT162b2	Pfizer-BioNTech COVID-19 vaccine
BSA	body surface area
CBER	Center for Biologics Evaluation and Research (United States)
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations (United States)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CTIS	Clinical Trial Information System
DCT	data collection tool
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form

Abbreviation	Term
EDB	exposure during breastfeeding
e-diary	electronic diary
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eICD	electronic informed consent document
EMA	European Medicines Agency
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)
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutinin inhibition assay
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
Ht	height
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IgG	immunoglobulin G
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
IRC	internal review committee

Abbreviation	Term
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
K	Proportionality constant for Schwartz equations (kidney function)
KDIGO	Kidney Disease: Improving Global Outcomes
LFT	liver function test
MDR	medical device regulation
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
mRNA	messenger ribonucleic acid
NA	neuraminidase
N/A	not applicable
NAAT	nucleic acid amplification test
NIMP	noninvestigational medicinal product
Omi	Omicron
PFS	prefilled syringe
PI	principal investigator
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RIV	recombinant influenza virus (Flublok Quadrivalent)
RNA	ribonucleic acid
S1	spike protein S1 subunit
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Screat	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
T bili	total bilirubin
Th1	T-helper type 1
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States

Abbreviation	Term
USADE	unanticipated serious adverse device effect
VE	vaccine efficacy
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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