A PHASE 1/2 MASTER PROTOCOL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF COMBINED MODIFIED RNA VACCINE CANDIDATES AGAINST COVID-19 AND INFLUENZA IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted by:	Pfizer
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Study Intervention Name:	Combination COVID-19 and Influenza modRNA Vaccine
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EudraCT/EU CT Number:	Not applicable
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Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5261001
Phase:	1/2

Brief Title:

A Study to Evaluate the Safety, Tolerability, and Immunogenicity of Combined Modified RNA Vaccine Candidates Against COVID-19 and Influenza

Document History

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Amendment 6	09 February 2024
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This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any PACL(s).

Protocol Amendment Summary of Changes Table

Amendment 6 (09 February 2024)

Overall Rationale for the Amendment:

Protocol revisions to remove participants ≥65 years of age from Substudy B and to revise Substudy A endpoints, moving Weeks 1 and 8 from primary to exploratory.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Throughout	Removed reference to initial-enrollment and expanded-enrollment groups	To align with removal of the ≥65-year age cohort in Substudy B	Substantial
Throughout	Corrected instances of COVID-19 and SARS-CoV-2 used incorrectly	To align with guidance to refer to the virus as SARS-CoV-2 and to the disease or vaccine as COVID-19	Nonsubstantial
Throughout	Updated mRNA to modRNA	To standardize across the protocol	Nonsubstantial
Throughout	Updated substudy headings to reflect the relevant substudy	To standardize across the protocol	Nonsubstantial
Title page	Updated title to reflect that this is a master protocol	To align with current guidance	Nonsubstantial
Throughout	Revised text to align with the removal of the initial-enrollment and expanded-enrollment groups	To align with removal of the ≥65-year age cohort in Substudy B	Substantial
Throughout	Removed any text referring to more than 1 dose (eg, "at least," "the first," "each dose")	To ensure that verbiage reflects only 1 vaccination in the studies	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 Synopsis	Removed cross-references to follow protocol template guidelines	To align with the protocol template	Nonsubstantial
Section 1.1 Synopsis and Section 2.1 Study Rationale	Added language regarding the WHO recommendation for the 2024-2025 influenza season	To align with formulations used in the study	Substantial
Sections 1.1 Synopsis and 10.12.6.1 Study Intervention(s) Administered for Substudy B	Removed arms containing placebo from Substudy B interventions	To align with removal of portions of Substudy B	Substantial
Sections 1.1 Synopsis, 10.11.3 Objectives, Endpoints, and Estimands (Substudy A), and 10.11.9 Statistical Considerations – Substudy A	Updated Substudy A objectives, endpoints, and estimands to move Week 1 and Week 8 immune responses to exploratory	Updated for new design	Nonsubstantial
Section 2.2.1 SARS-CoV-2	Removed language regarding XBB	To align with removal of Substudy C	Substantial
Section 2.2.3.2 Influenza	Added language to update current C4781004 study numbers as well as to remove A and B strain information that was not necessary for this study	To update current numbers and align with what is used in this study	Nonsubstantial
Section 6 Study Intervention(s) and Concomitant Therapy	Updated Table 2 to reflect vaccines used in the studies	To align with what was used in each study	Nonsubstantial
Section 10.1.6 Dissemination of Clinical Study Data	Added website information for ClinicalTrials.gov and Pfizer.	To align with the current protocol template	Nonsubstantial
Section 10.10.4 Recording/Reporting and Follow-Up of Medical Device Deficiencies	Updated language to the current protocol template	To align with the current protocol template	Nonsubstantial
Section 10.5.2 Female Participant Reproductive Inclusion Criteria	Added the section	To align with updates to the protocol template	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1/2 Master Protocol to Evaluate the Safety, Tolerability, and Immunogenicity of Combined Modified RNA Vaccine Candidates Against COVID-19 and Influenza in Healthy Individuals

Brief Title:

A Study to Evaluate the Safety, Tolerability, and Immunogenicity of Combined Modified RNA Vaccine Candidates Against COVID-19 and Influenza

Regulatory Agency Identification Number(s):

US IND Number:	28917
EudraCT/EU CT Number:	Not applicable
ClinicalTrials.gov ID:	NCT05596734
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5261001
Phase:	1/2

Rationale:

This master protocol describes the investigational plan of a combination vaccine containing modified RNA components encoding proteins of the SARS-CoV-2 prefusion spike and influenza HA antigens. This combination vaccine aims to simplify vaccination practices for the prevention of 2 potentially serious respiratory illnesses: influenza and COVID-19.

BNT162b2 (Comirnaty®) is a modRNA-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. 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. From 18 April 2023 until 11 September 2023, the bivalent original*/Omicron BA.4/BA.5 COVID-19 vaccine had been authorized for use for all doses administered to individuals 6 months of age and older.

All versions of the vaccine encode the SARS-CoV-2 prefusion spike protein(s) in modRNA encapsulated in RNA-LNPs, which has demonstrated potent immunogenicity, high 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. Therefore, bivalent BNT162b2

(original*/Omi BA.4/BA.5), consisting of the original SARS-CoV-2 prefusion spike protein modRNA, targeting the ancestral strain of the virus, in combination with modRNA encoding the spike protein of the Omicron variant (BA.4/BA.5 sublineage), will be used in this study.

Pfizer also has a quadrivalent modRNA-based influenza vaccine, qIRV, currently in Phase 3 development. qIRV encodes the HA antigen of [redacted] influenza strains ([redacted]) recommended seasonally by WHO for the influenza season. Based on Phase 2 safety and **immunogenicity** data, the dose level of qIRV being studied in the Phase 3 C4781004 study, by age stratum, is [redacted] µg for participants 18 through 64 years of age and [redacted] µg for participants ≥65 years of age.

The WHO recommendation for the composition of influenza vaccines in the 2023-2024 northern hemisphere influenza season includes both a quadrivalent vaccine and a trivalent vaccine, the latter without the B/Yamagata lineage, which has not been seen in circulation since March 2020. Based on the 05 October 2023 VRBPAC recommendations, the committee voted to exclude the B/Yamagata lineage antigen component from quadrivalent influenza vaccines as soon as possible. The study design therefore includes a quadrivalent influenza vaccine (qIRV) and a trivalent influenza vaccine (tIRV) when combined with BNT162b2 (the Pfizer-BioNTech COVID-19 vaccine).

Given that annual vaccine programs in the US and likely other parts of the world against both influenza and COVID-19 may be conducted in the future at a similar time of year, developing a combined vaccine targeting both viruses is likely to generate overall higher vaccination rates for both viruses by allowing for more convenient scheduling than if these vaccines were to be administered separately. Hence, this study will evaluate the safety, tolerability, and immunogenicity of a modRNA vaccine against influenza when combined with BNT162b2 (bivalent original*/Omi BA.4/BA.5). This evaluation will initially be conducted through the following substudies:

- Substudy A: A Phase 1 substudy in up to approximately 360 participants (180 participants 18 through 64 years of age and 180 participants ≥65 years of age) to describe the safety of qIRV and bivalent BNT162b2 (original*/Omi BA.4/BA.5) at 3 dose-level combinations.

- Substudy B: A Phase 1/2 substudy to describe the safety and immunogenicity of IRV (qIRV or tIRV) when administered in combination with bivalent BNT162b2 (original*/Omi BA.4/BA.5), and licensed QIV given concurrently with bIRV/bivalent BNT162b2 (original*/Omi BA.4/BA.5) in healthy adults 18 through 64 years of age.

* Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Based on preliminary data from Substudy A, Substudy B will study additional combinations of COVID-19/influenza modRNA vaccines, including tIRV: [redacted] µg [redacted] plus [redacted] µg bivalent BNT162b2 (original/Omi BA.4/BA.5), bIRV: [redacted] µg [redacted] plus

[redacted]µg bivalent BNT162b2 (original/Omi BA.4/BA.5) given concurrently with QIV in the opposite arm, and additional novel combinations of qIRV [redacted]µg [redacted]. This is supported by an acceptable tolerability profile for a dose up to [redacted]µg of a combination of influenza modRNA and COVID-19 modRNA, with opportunity to increase the immune response against both COVID-19 and influenza strains.

Following a thorough review of safety data from Substudy A for both the 18- through 64-year age group and the ≥65-year age group by the sponsor's IRC in March 2023 and May 2023, continued use of COVID-19/influenza combination vaccines up to [redacted]µg maximum RNA dose was considered acceptable for continuation into Substudy B.

Objectives, Endpoints, and Estimands:

Substudy A (Phase 1)		
Objectives	**Estimands**	**Endpoints**
Primary Safety	**Primary Safety**	**Primary Safety**
To describe the safety and tolerability of qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at various dose-level combinations in participants ≥18 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately and combined, receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs from vaccination through 4 weeks after vaccination • SAEs from the first vaccination through 6 months after vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	The percentage of participants with: • Abnormal troponin I laboratory values 2 days and 1 week after vaccination	Troponin I laboratory parameters detailed in the protocol
	The percentage of participants with: • New ECG abnormalities 2 days and 1 week after vaccination	ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in the protocol
Secondary	**Secondary**	**Secondary**
To describe the immune responses elicited by qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at various dose-level combinations in participants ≥18 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately, complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 4 weeks after vaccination • GMFR from before vaccination to 4 weeks after vaccination • The proportion of participants achieving HAI seroconversion[a] for each strain at 4 weeks after vaccination • The percentage of participants with HAI titers ≥1:40 for each strain before vaccination and at 4 weeks after vaccination • The percentage of participants achieving HAI seroconversion for all strains at 4 weeks after vaccination • The percentage of participants with HAI titers ≥1:40 for all strains at 4 weeks after vaccination	HAI titers for the matched seasonal strains (CCI recommended by WHO

Substudy A (Phase 1)		
Objectives	**Estimands**	**Endpoints**
	In participants 18 through 64 years of age and ≥65 years of age, separately, having received qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) and complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 4 weeks after vaccination for each strain • GMFR from before vaccination to 4 weeks after vaccination for each strain • Percentages of participants with seroresponse[b] at 4 weeks after vaccination for each strain	• SARS-CoV-2 Omicron BA.4/BA.5–neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
Exploratory	**Exploratory**	**Exploratory**
To describe the immune responses elicited by qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at various dose-level combinations in participants ≥18 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately, complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 1 and 8 weeks after vaccination • GMFR from before vaccination to 1 week after vaccination • The proportion of participants achieving HAI seroconversion[a] for each strain at 1 and 8 weeks after vaccination • The percentage of participants with HAI titers ≥1:40 for each strain before vaccination and at 1 and 8 weeks after vaccination • The percentage of participants achieving HAI seroconversion for all strains at 1 and 8 weeks after vaccination • The percentage of participants with HAI titers ≥1:40 for all strains at 1 and 8 weeks after vaccination	HAI titers for the matched seasonal strains CCI recommended by WHO
To describe the immune responses elicited by qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at various dose-level combinations in participants ≥18 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately, having received qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) and complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 1 and 8 weeks after vaccination for each strain • GMFR from before vaccination to 1 and 8 weeks after vaccination for each strain • Percentages of participants with seroresponse[b] at 1 and 8 weeks after vaccination for each strain	• SARS-CoV-2 Omicron BA.4/BA.5–neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers

Substudy A (Phase 1)		
Objectives	**Estimands**	**Endpoints**
To describe the immune response to emerging VOCs in participants ≥18 years of age		• SARS-CoV-2 neutralizing titers for VOCs not already specified

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

Substudy B (Phase 1/2)

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
To describe the safety and tolerability of study interventions in participants 18 through 64 years of age	In participants 18 through 64 years of age receiving at least 1 dose of study intervention, the percentage of participants with: • Abnormal troponin I laboratory values 2 days and 1 week after vaccination	• Troponin I laboratory parameters detailed in the protocol
	In participants 18 through 64 years of age receiving at least 1 dose of study intervention, the percentage of participants with: • New ECG abnormalities 2 days and 1 week after vaccination	• ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in the protocol
	In participants 18 through 64 years of age receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following vaccination in the right arm only • Systemic events for up to 7 days following vaccination in the right arm • AEs from vaccination through 4 weeks after each vaccination • SAEs from vaccination through 6 months after the first vaccination	• Local reactions (pain at the injection site, redness, and swelling) in the right arm only • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Immunogenicity[a]	**Secondary Immunogenicity[a]**	**Secondary Immunogenicity[a]**
To describe the immune responses to SARS-CoV-2 and influenza elicited by each study intervention	In participants 18 through 64 years of age complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at each blood sampling time point after influenza vaccination • GMFR from before vaccination to each blood sampling time point after influenza vaccination • The proportion of participants achieving HAI seroconversion[b] for each strain at each blood sampling time point after influenza vaccination • The percentage of participants with HAI titers ≥1:40 for each strain before vaccination and at each blood sampling time point after influenza vaccination	• HAI titers for the matched seasonal strains recommended by WHO

Substudy B (Phase 1/2)

Objectives	Estimands	Endpoints
	In participants 18 through 64 years of age complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at each blood sampling time point after vaccination for each strain • GMFR from before SARS-CoV-2 vaccination to each blood sampling time point after vaccination for each strain • Percentages of participants with seroresponse[c] at each blood sampling time point after SARS-CoV-2 vaccination for each strain	• SARS-CoV-2–neutralizing titers by strain
Tertiary/Exploratory	**Tertiary/Exploratory**	**Tertiary/Exploratory**
To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern) in participants 18 through 64 years of age	As detailed in the SAP	• SARS-CoV-2 neutralizing titers for emerging variants (under monitoring, of interest, and/or of concern)
To describe the troponin and ECG abnormalities detected in participants who are evaluated for possible cardiac symptoms	As detailed in the SAP	• Troponin I laboratory parameters detailed in the protocol • ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in the protocol

a. There are no primary immunogenicity objectives in this study.
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 at least a 4-fold rise at the time point of interest.
c. 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.

Overall Design:

This study includes 2 substudies (Substudies A and B).

Substudies A and B are designed to describe the safety, tolerability, and immunogenicity of several vaccines that include combined or standalone modRNA encoding 3 or 4 influenza strains* and/or modRNA encoding 1 or more SARS-CoV-2 strains. The study interventions evaluated in Substudy A are shown in the table titled Substudy A: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations. The study interventions evaluated in Substudy B are shown in the table titled Substudy B: All Vaccine Groups.

Each of these substudies includes the use of licensed/authorized standalone influenza vaccine (QIV) and COVID-19 vaccines as comparators. In Substudy A and Substudy B, bivalent BNT162b2 (original/Omi BA.4/BA.5) represents the COVID-19 comparator. Bivalent BNT162b2 (original/Omi BA.4/BA.5) used in Substudies A and B was recommended by ACIP in 2022-2023. In Substudy A, the QIV comparator is Fluzone SD. In Substudy B, the QIV comparator is Flucelvax.

* Influenza strains used in Substudy A and Substudy B were based on the WHO recommendations for use in the northern hemisphere in 2022-2023.

Substudy A: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations

Dose-Level Combination	qIRV Dose	Bivalent BNT162b2 (Original/ Omi BA.4/BA.5) Dose	Total modRNA Dose
1	CCI µg, ie, CCI	CCI µg, ie, • CCI µg of original BNT162b2 and • µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)	CCI µg
2	CCI µg, ie, CCI	CCI µg, ie, • CCI µg of original BNT162b2 and • µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)	CCI µg
3	CCI µg, ie, CCI	CCI µg, ie, • CCI µg of original BNT162b2 and • µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)	CCI µg

Substudy B: All Vaccine Groups							
Substudy B Vaccine Group	qIRV/Bivalent BNT162b2 Dose-Level Combinations[a]	qIRV, tIRV, or bIRV	Bivalent BNT162b2[b]	Licensed QIV	LNP Dose	Total modRNA Dose	Approximate Number of Participants
1	N/A	N/A	CCI µg	Licensed QIV	CCI mg	CCI µg	30
2[c]	N/A	CCI µg bIRV (CCI)	µg	Licensed QIV	mg	µg	30
3	1	CCI µg qIRV (CCI)	µg	N/A	mg	µg	120
4[d]	2	CCI µg qIRV (CCI (CCI)	CCI µg	N/A	mg	µg	120
5	3	CCI µg qIRV (CCI)	CCI µg	N/A	mg	µg	120
6	4	CCI µg qIRV (CCI)	µg	N/A	mg	µg	30
7	5	CCI µg qIRV (CCI)	µg	N/A	mg	µg	30
8	6	CCI µg qIRV (CCI)	µg	N/A	mg	µg	30
9	7	CCI µg qIRV (CCI)	µg	N/A	mg	µg	30
10	8	CCI µg qIRV (CCI)	µg	N/A	mg	µg	30

Substudy B: All Vaccine Groups							
Substudy B Vaccine Group	**qIRV/Bivalent BNT162b2 Dose-Level Combinations[a]**	**qIRV, tIRV, or bIRV**	**Bivalent BNT162b2[b]**	**Licensed QIV**	**LNP Dose**	**Total modRNA Dose**	**Approximate Number of Participants**
11[c]	N/A	[redacted]µg tIRV ([redacted])	[redacted]µg	N/A	[redacted]mg	[redacted]µg	30
12[d]	N/A	qIRV ([redacted])	N/A	N/A	[redacted]mg	[redacted]µg	30

a. For qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) that is [redacted] mIRVs encoding HA for each A and B strain will be [redacted] to generate qIRV at the dose-level combination shown; the resultant qIRV will then be [redacted] with bivalent BNT162b2 (original/Omi BA.4/BA.5) prior to administration. Please see the IPM for further details.

b. For bivalent BNT162b2 formulations: [redacted]µg total dose includes [redacted]µg of Omicron BA.4/BA.5 and [redacted]µg of the ancestral SARS-CoV-2 strain; [redacted]µg total dose includes [redacted]µg of Omicron BA.4/BA.5 and [redacted]µg of the ancestral SARS-CoV-2 strain. Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

c. Groups 2 and 11: bIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) and tIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) are [redacted]

d. Groups 4 and 12: qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) and qIRV are [redacted]

Note: The following influenza strains are included in the IRV in each group at the dose level noted:
Group [redacted]
Groups [redacted] through [redacted] and [redacted]
Group [redacted]
Group [redacted]

Substudy A (Phase 1)

This is a Phase 1 randomized, open-label substudy to describe the safety and immunogenicity of up to 3 dose-level combinations of qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5). Approximately 360 participants will be enrolled across 2 age strata: approximately 180 participants 18 through 64 years of age and approximately 180 participants ≥65 years of age will be randomized equally (approximately 30 participants per group) to each group to receive a dose of either:

- qIRV/bivalent BNT162b2 (original*/Omi BA.4/BA.5), at 1 of the 3 dose-level combinations shown in the table above titled Substudy A: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations,
- [redacted] µg qIRV,
- [redacted] µg qIRV, or
- [redacted] µg Bivalent BNT162b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to licensed QIV

* Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Safety and immunogenicity data from studies previously conducted in participants of a similar age range having received 1 dose of BNT162b2 at a dose level of [redacted] µg and [redacted] µg may be used as a control during the substudy analysis.

Enrollment in each age stratum will be controlled such that no more than 10 participants (sentinel ≤10 participants) can be vaccinated on the first day; vaccination of the remaining participants will commence no sooner than 24 hours after the tenth participant received his or her vaccination.

Stopping rules for participants in Substudy A will apply to groups receiving the combination bivalent BNT162b2 (original/Omi BA.4/BA.5) and qIRV as detailed in the protocol.

After confirmation of eligibility by the investigator, participants will be enrolled, randomized, and will receive administration of 1 or 2 doses of study intervention. Where 2 doses of study intervention are given, 1 dose will be given in each arm. All study interventions will be administered via intramuscular injection into the deltoid muscle.

All participants will be asked to complete a reactogenicity e-diary for 7 days following each vaccination. Blood samples of approximately 50 mL will be collected for immunogenicity assessments prior to Vaccination 1 and at 1, 4, and 8 weeks after vaccination. All participants will be asked to provide an additional blood sample of approximately 2.5 mL at time points specified in the protocol for assessment of troponin I.

Safety and immunogenicity data accumulated for at least 4 weeks following vaccination in each age stratum will be reviewed by the sponsor's IRC to determine if enrollment in each age stratum of Substudy B may proceed. Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, subsequent collection of blood samples from participants in that group may be halted and/or blood samples may not be analyzed, and study visits or other procedures may be discontinued.

The total duration of the study for each participant will be up to approximately 6 months.

Substudy B (Phase 1/2)

This is a Phase 1/2 substudy to describe the safety, tolerability, and immunogenicity of IRV (qIRV, tIRV, or bIRV) when administered in combination with bivalent BNT162b2 (original/Omi BA.4/BA.5). Bivalent BNT162b2 (original/Omi BA.4/BA.5) will be used during the substudy, as detailed in the table titled Substudy B: All Vaccine Groups. Substudy B will be single-blind (sponsor-unblinded). In Substudy B, up to approximately 630 participants 18 through 64 years of age will be enrolled. Randomization will be conducted across 3 enrollment cohorts independently due to licensed QIV availability, with enrollment in these cohorts being conducted either concurrently or at different times as required based on operational considerations, as shown in the table below.

Substudy B: Enrollment Cohorts				
Enrollment Cohort	**Total Number of Participants**	**Number of Participants per Vaccine Group**	**Vaccine Group Number**	**Vaccine Group Descriptions**
1	60	30	1	Licensed QIV (Flucelvax) administered concurrently in the opposite arm to [redacted] µg bivalent BNT162b2 (original*/Omi BA.4/BA.5)
			2	Licensed QIV (Flucelvax) administered concurrently in the opposite arm to bIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)
2	360	Up to 120	3	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 1[a]
			4	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 2[a]
			5	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 3[a]

Substudy B: Enrollment Cohorts				
Enrollment Cohort	**Total Number of Participants**	**Number of Participants per Vaccine Group**	**Vaccine Group Number**	**Vaccine Group Descriptions**
3	210	30	6	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 4[a]
			7	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 5[a]
			8	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 6[a]
			9	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 7[a]
			10	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 8[a]
			11	tIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)
			12	qIRV

a. Combination as shown in the table titled Substudy B: All Vaccine Groups.

Note: * Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Enrollment of participants (Groups 2, 6, 7, 8, 9, 10, 11, and 12) will be controlled such that no more than 10 participants (sentinel participants) can be vaccinated on the first day; vaccination of the remaining participants will commence no sooner than 24 hours after this safety pause.

Stopping rules will apply to all groups as detailed in the protocol.

Safety data accumulated at least 4 weeks following vaccination of participants 18 through 64 years of age in Substudy B will be reviewed by the sponsor's IRC, and if these data are deemed acceptable, the IRC will evaluate which groups (as detailed in the table titled Substudy B: Enrollment Cohorts above) are acceptable for further study.

Immunogenicity Blood Draws in Substudy B:

Blood samples of approximately 15 mL will be collected for immunogenicity assessments prior to vaccination and at 4 weeks after vaccination. Up to 20 participants in Groups 3, 4, and 5 in the 18- through 64-year age stratum will be asked to consent to alternatively providing 50-mL, rather than 15-mL, blood samples at the same time points, which will be used for immunogenicity assessments as well as assay development/maintenance.

For Substudy B blood draws (as detailed above), the higher-volume blood draws of 50 mL will be done in up to 20 participants who are enrolled first and give consent.

All participants will be asked to complete a reactogenicity e-diary for 7 days following each vaccination.

Following vaccination, AEs will be collected from informed consent signing through 4 weeks following each vaccination, and SAEs will be collected from informed consent signing through 6 months after the first vaccination. In addition, AEs will be collected that occur up to 48 hours after blood draws.

Number of Participants:

Up to approximately 990 participants will be enrolled across all substudies.

Substudy A (Phase 1)

Up to approximately 360 participants (n=30 per dose level per group) will be enrolled across 2 age strata: approximately 180 participants 18 through 64 years of age and approximately 180 participants ≥65 years of age in Substudy A.

Substudy B (Phase 1/2)

Up to approximately 630 participants 18 through 64 years of age will be enrolled in Substudy B.

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

Study Population:

Substudy A (Phase 1)

Inclusion Criteria

Inclusion criteria for Substudy A can also be found in the protocol.

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

Age and Sex:

1. Male or female participants ≥18 years of age (or the minimum age of consent in accordance with local regulations) at Visit 1 (Day 1).
    - Refer to Appendix 5 for reproductive criteria for male and female participants in the protocol.

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

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

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

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

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. **For participants 18 through 64 years of age:** participants who have received 3 prior doses of 30 µg BNT162b2, with the last dose being 150 days to 365 days before Visit 1 (Day 1).

   For participants ≥65 years of age: participants who have received 4 or 5 prior doses of a modRNA SARS-CoV-2 vaccine, with the last dose being a bivalent vaccine, 90 days to 365 days before Visit 1 (Day 1).

   Note: Documented confirmation of prior doses of modRNA SARS-CoV-2 vaccines received must be obtained prior to randomization.

6. **For participants ≥65 years of age:** receipt of licensed influenza vaccination for the 2022-2023 northern hemisphere season ≥120 days before study intervention administration.

Exclusion Criteria

Exclusion criteria for Substudy A can also be found in the protocol.

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

Medical Conditions:

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

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

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

4. Women who are pregnant or breastfeeding.

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

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

Prior/Concomitant Therapy:

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

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

9. **For participants 18 through 64 years of age:** vaccination with any investigational or licensed influenza vaccine within 6 months (175 days) before study intervention administration.

Prior/Concurrent Clinical Study Experience:

10. Participation in other studies involving a study intervention within 28 days before randomization. Anticipated participation in other studies within 28 days after receipt of study intervention in this study.

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

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

12. Participation in strenuous or endurance exercise through Visit 3.

13. Prior history of heart disease.

14. Any abnormal screening troponin I laboratory value.

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

Substudy B (Phase 1/2)

Inclusion Criteria

Inclusion criteria for Substudy B can also be found in the protocol.

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

Age and Sex:

1. Male or female participants 18 through 64 years of age (or the minimum age of consent in accordance with local regulations) at Visit 201 (Day 1).

    - Refer to Appendix 5 for reproductive criteria for male and female participants in the protocol.

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

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

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

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

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. Participants who have received at least 3 prior US-authorized modRNA COVID-19 vaccines, with the last dose being an updated (bivalent) vaccine given at least 150 days before Visit 201 (Day 1). Any dose of modRNA COVID-19 vaccine received after 01 September 2022 may be considered to be a bivalent vaccine in the US.

Note: Documented confirmation of prior doses of SARS-CoV-2 vaccine received must be obtained prior to randomization.

Exclusion Criteria

Exclusion criteria for Substudy B can also be found in the protocol.

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

Medical Conditions:

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

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

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

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

5. Women who are pregnant or breastfeeding.

6. History of myocarditis or pericarditis.

Prior/Concomitant Therapy:

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

8. 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 60 days before study intervention administration, or planned receipt throughout the study.

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

Prior/Concurrent Clinical Study Experience:

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

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

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

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

12. Participation in strenuous or endurance exercise through Visit 203.

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

14. Any abnormal screening troponin I laboratory value.

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

Study Arms and Duration:

Study Interventions Administered

Substudy A (Phase 1)

The total duration of Substudy A for each participant will be up to approximately 6 months. Study interventions for Substudy A will include:

Intervention Name	Bivalent BNT162b2 (original[a]/Omi BA.4/BA.5) (original BNT162b2 and BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5]) CCI [redacted]	qIRV	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5)	QIV
Arm Name (group of participants receiving a specific study intervention or no study intervention)	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) or Licensed QIV+bivalent BNT162b2 (original/ Omi BA.4/BA.5)	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) or CCI [redacted] µg qIRV or CCI [redacted] µg qIRV	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5)	Licensed QIV + bivalent BNT162b2 (original/Omi BA.4/BA.5)
Targeted Influenza Strains	N/A	For each season, strains as recommended by WHO for recombinant or cell-based influenza vaccines	For each season, strains as recommended by WHO for recombinant or cell-based influenza vaccines	For each season, strains as recommended by WHO
Type	Vaccine	Vaccine	Vaccine	Vaccine
Dose Formulation	modRNA	modRNA	modRNA	
Unit Dose Strength(s)	As detailed in the IPM	As detailed in the IPM	As detailed in the IPM	As detailed in the IPM

Dosage Level(s)	CCI µg or CCI µg (CCI µg original BNT162b2 and CCI µg BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5]) (CCI µg original BNT162b2 and CCI µg BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5])	CCI µg (CCI µg per strain) CCI µg CCI µg per strain)	Dose-level combination 1 as shown in the table titled Substudy A: qIRV/Bivalent BNT162b2 (Original/ Omi BA.4/BA.5) Dose-Level Combinations CCI µg qIRV CCI µg (CCI µg per strain) BNT162b2 CCI µg (CCI µg original BNT162b2 and CCI µg BNT162b2 Omicron [B.1.1.529 subline age BA.4/BA.5]) Dose-level combination 2 as shown in the table titled Substudy A: qIRV/Bivalent BNT162b2 (Original/ Omi BA.4/BA.5) Dose-Level Combinations CCI µg qIRV CCI µg (CCI µg per strain) BNT162b2 CCI µg (CCI µg original BNT162b2 and CCI µg BNT162b2 Omicron [B.1.1.529 subline age BA.4/BA.5]) Dose-level combination 3 as shown in the table titled Substudy A: qIRV/Bivalent BNT162b2 (Original/	

			Omi BA.4/BA.5) Dose-Level Combinations [redacted]µg qIRV [redacted]µg ([redacted]µg per strain) BNT162b2 [redacted]µg ([redacted]µg original BNT162b2 and [redacted]µg BNT162b2 Omicron [B.1.1.529 subline age BA.4/BA.5])	
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Comparator
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by Pfizer	Provided centrally by Pfizer	Study intervention will be generated by mixing the following at the site at the dose-level combinations detailed above: • qIRV • Bivalent BNT162b2 (original/Omi BA.4/BA.5)	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.		Study intervention will be provided as either a PFS or a glass vial as open-label supply. Each vial will be labeled per country requirement.

a. Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Substudy A (Phase 1)

Study arms for Substudy A will include:

Study Arms						
Group Number	**1**	**2**	**3**	**4**	**5**	**6**
Arm Title	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) Dose-level combination 1 as shown in the table titled Substudy A: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) Dose-level combination 2 as shown in the table titled Substudy A: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) Dose-level combination 3 as shown in the table titled Substudy A: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations	[redacted] µg qIRV	[redacted] µg qIRV	Licensed QIV+ bivalent BNT162b2 (original/Omi BA.4/BA.5)
Arm Type	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants will receive qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 1 as shown in the table titled Substudy A: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations	Participants will receive qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 2 as shown in the table titled Substudy A: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations	Participants will receive qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 3 as shown in the table titled Substudy A: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations	Participants will receive [redacted] µg of qIRV	Participants will receive [redacted] µg of qIRV	Participants will receive [redacted] µg of bivalent BNT162b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to QIV
Associated Intervention Labels	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)	qIRV	qIRV	Bivalent BNT162b2 (original/Omi BA.4/BA.5) and QIV

Substudy B (Phase 1/2)

The total duration of Substudy B for each participant will be up to approximately 6 months from the first vaccination. Study interventions for Substudy B will include:

Intervention Name	BNT162b2[a] CCI	qIRV	qIRV[b]/BNT162b2[a]	tIRV[c]/BNT162b2[a]	bIRV[c]/BNT162b2[a]	QIV
Arm Name (group of participants receiving a specific study intervention or no study intervention)	Licensed QIV + BNT162b2[a]	qIRV	qIRV/BNT162b2[a]	tIRV/BNT162b2[a]	bIRV/BNT162b2[a] + licensed QIV	Licensed QIV + BNT162b2 a or Licensed QIV + bIRV/BNT162b2a
Targeted Influenza Strains	N/A	Strains as recommended by WHO for recombinant or cell-based influenza vaccines	Strains as recommended by WHO for recombinant or cell-based influenza vaccines	Strains as recommended by WHO for recombinant or cell-based influenza vaccines	Strains as recommended by WHO for recombinant or cell-based influenza vaccines	For each seasonal strain as recommended by WHO
Type	modRNA vaccine	modRNA vaccine	modRNA vaccine	modRNA vaccine	modRNA vaccine	Vaccine
Dose Formulation	modRNA	modRNA	modRNA	modRNA	modRNA	
Unit Dose Strength(s)	CCI µg BNT162b2[a]	CCI µg qIRV for participants 18 through 64 years of age (as detailed in the IMP)	CCI µg or CCI µg or CCI µg in dose-level combinations as described in the tables titled Substudy B: All I Vaccine Groups	CCI µg tIRV/ CCI µg BNT162b2[a]	CCI µg bIRV/ CCI µg BNT162b2[a]	CCI µg bIRV/ CCI µg BNT162b2[a] As detailed in the IPM
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection

Use	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided 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. Each PFS or vial will be labeled per country requirement.

a. Bivalent BNT162b2 (original*/Omi BA.4/BA.5) will be used during Substudy B. *Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.
b. Will have formulations that are CCI [redacted] per the IPM and CCI [redacted]
c. Formulations will be CCI [redacted]

Statistical Methods:

Substudy A (Phase 1)

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

Safety and immunogenicity data from studies previously conducted in participants of a similar age range having received 1 dose of BNT162b2 at a dose level of [redacted] µg and [redacted] µg may be used as a control during the study analysis.

The primary safety objective for the study will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each vaccine group by age stratum (18 through 64 and ≥65 years of age) and overall (≥18 years of age). Abnormal troponin I laboratory parameters and ECG abnormalities consistent with probable or possible myocarditis or pericarditis will also be descriptively summarized for by age stratum (18 through 64 and ≥65 years of age) and overall (≥18 years of age).

The secondary (immunogenicity) objective will be evaluated descriptively by age stratum (18 through 64 and ≥65 years of age) by GMT and GMFR of both HAI and SARS-CoV-2 neutralizing titers, as well as:

- the percentage of participants achieving seroconversion measured by HAI, and proportion of participants with HAI titers ≥1:40, for each strain at the various time points.
- the percentage of participants with seroresponse of SARS-CoV-2 neutralizing titers at the various time points.

Substudy B (Phase 1/2)

There is no formal sample size calculation for the planned sample size in Substudy B, as there is no formal hypothesis testing.

The immunogenicity objectives will be evaluated descriptively by GMT, GMFR, percentage of participants achieving seroconversion, percentage of participants with seroresponse, and the associated 95% CIs, at the various time points.

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

Ethical Considerations:

The available safety and immunogenicity data from ongoing clinical trials and real-world effectiveness and safety data for BNT162b2, combined with available nonclinical data with BNT162 vaccines, as well as data from nonclinical and clinical trials with qIRV, support a favorable benefit/risk profile and support clinical development of a vaccine combining these components. Taking into account the measures to minimize risk to study participants, the potential risks identified in association with the study intervention are justified by the anticipated benefits that may be afforded to healthy participants.

As IRV formulations (bIRV, tIRV, and qIRV) and bivalent BNT162b2 (original/Omi BA.4/BA.5) have the same modRNA and LNP platform as BNT162b2, their safety profiles are expected to be similar to that of BNT162b2. Based on the experience with BNT162b2, the potential risks for IRV formulations combined with bivalent BNT162b2 (original/Omi BA.4/BA.5) include the following:

- Local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fever, fatigue, headache, chills, muscle pain, and joint pain.
- Very rare cases of myocarditis and pericarditis have been reported after authorization in recipients of BNT162b2.
- Cases of anaphylaxis have been reported; however, the frequency is not estimable from the available data.

The study procedure–related risks include the following:

- Venipuncture will be performed during the study.

1.2. Schema

Substudy B Schema:

Substudy B	Enrollment Cohort 1		Enrollment Cohort 2	Enrollment Cohort 3	
Age Stratum 18-64 Years	Vaccine group[a] 1 (n = ~30) Vaccine group[a] 2 (n = ~30)		Vaccine group[a] 3 (n= ~≤120) Vaccine group[a] 4 (n= ~≤120) Vaccine group[a] 5 (n= ~≤120)	Vaccine group[a] 6 (n = ~30) Vaccine group[a] 7 (n = ~30) Vaccine group[a] 8 (n = ~30) Vaccine group[a] 9 (n = ~30) Vaccine group[a] 10 (n = ~30) Vaccine group[a] 11 (n = ~30) Vaccine group[a] 12 (n = ~30)	
	Sentinel[b] ≤10 participants from group 2 →	Full ~50 participants	Full ~330 participants →	Sentinel[b] ≤10 participants per group →	Full ~140 participants

a. Please see Table 2 for details on the vaccine groups.
b. A safety review will be conducted on 24 hours of postvaccination safety data from sentinel participants before full enrollment of the remaining participants in each vaccine group, with the exception of Groups 1, 3, 4, and 5, as enrollment of those groups occurred under a prior protocol version.

Note: The arrow represents the 24-hour safety pause.

1.3. Schedule of Activities

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

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

See Section 10.11.1 for the Substudy A SoA.

See Section 10.12.1 for the Substudy B SoA.

2. INTRODUCTION

2.1. Study Rationale

This master protocol describes the investigational plan of a combination vaccine containing modified RNA components encoding proteins of the SARS-CoV-2 prefusion spike and influenza HA antigens. This combination vaccine aims to simplify vaccination practices for the prevention of 2 potentially serious respiratory illnesses: influenza and COVID-19.

BNT162b2 (Comirnaty®) is a modRNA-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.[1] 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.[2]

From 18 April 2023 until 11 September 2023, the bivalent original*/Omicron BA.4/BA.5 COVID-19 vaccine had been authorized for use for all doses administered to individuals 6 months of age and older.[3]

* Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

A bivalent formulation of the vaccine BNT162b2 (bivalent BNT162b2 [original/Omi BA.4/BA.5]) has been granted EUA in the US as a single booster dose in individuals 12 years of age and older, to be administered at least 2 months after either completion of primary vaccination or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 vaccine.[4]

All versions of the vaccine encode the SARS-CoV-2 prefusion spike protein(s) in modRNA encapsulated in RNA-LNPs, which has demonstrated potent immunogenicity, high VE, and a favorable safety profile in Phase 1, 2, and 3 human trials,[5] as well as in real-world usage.[6] As SARS-CoV-2 continues to circulate,[7] 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. Therefore, bivalent BNT162b2 (original/Omi BA.4/BA.5), consisting of the original SARS-CoV-2 prefusion spike protein modRNA, targeting the ancestral strain of the virus, in combination with modRNA encoding the spike protein of the Omicron variant (BA.4/BA.5 sublineage), will be used in this study.

Pfizer also has a quadrivalent modRNA-based influenza vaccine, qIRV, in Phase 3 development. qIRV encodes HA of CCI strains (CCI) seasonally recommended by WHO for the influenza season.[8] Based on Phase 2 safety and immunogenicity data, the dose level of qIRV being studied in the Phase 3 C4781004 protocol by age stratum is CCI µg for participants 18 through 64 years of age and CCI µg for participants ≥65 years of age.

The WHO recommendation for the composition of influenza vaccines in the 2024-2025 northern hemisphere influenza season includes both a quadrivalent vaccine and a trivalent vaccine, the latter without the B/Yamagata lineage, which has not been seen in circulation since March 2020. Based on the 05 October 2023 VRBPAC recommendations, the committee voted to exclude the B/Yamagata lineage antigen component from quadrivalent influenza vaccines as soon as possible.[9] The study design therefore includes a quadrivalent influenza vaccine (qIRV) and a trivalent influenza vaccine (tIRV) when combined with BNT162b2 (the Pfizer-BioNTech COVID-19 vaccine).

Given that annual vaccine programs in the US and likely other parts of the world against both influenza and SARS-CoV-2 may be conducted in the future at a similar time of year, developing a combined vaccine targeting both viruses is likely to generate overall higher vaccination rates for both viruses by allowing for more convenient scheduling than if these vaccines were to be administered separately. Hence, this study will evaluate the safety, tolerability, and immunogenicity of a modified RNA vaccine against influenza when combined with BNT162b2 (bivalent original/Omi BA.4/BA.5). This evaluation will initially be conducted through the following substudies:

- Substudy A: A Phase 1 substudy in up to approximately 360 participants (180 participants 18 through 64 years of age and 180 participants ≥65 years of age) to describe the safety of qIRV and bivalent BNT162b2 (original/Omi BA.4/BA.5) at 3 dose-level combinations as shown in Table 1.

- Substudy B: This is an exploratory Phase 1/2 substudy to describe the safety and immunogenicity of IRV (qIRV, tIRV, or bIRV) when administered in combination with bivalent BNT162b2 (original/Omi BA.4/BA.5), and licensed QIV given concurrently with bIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) in healthy adults 18 through 64 years of age. Based on preliminary data from Substudy A, Substudy B will study additional combinations of COVID-19/influenza modRNA vaccines, including tIRV: CCI µg (CCI) plus CCI µg bivalent BNT162b2 (original/Omi BA.4/BA.5); bIRV: CCI µg (CCI) plus CCI µg bivalent BNT162b2 (original/Omi BA.4/BA.5) given concurrently with QIV in the opposite

arm; and additional novel combinations of qIRV: [CCI] µg ([CCI]).

Following a thorough review of safety data from Substudy A for both the 18- through 64-year age group and the ≥65-year age group by the sponsor's IRC in March 2023 and May 2023, continued use of COVID-19/influenza combination vaccines up to [CCI] µg maximum RNA dose was considered acceptable for continuation into Substudy B.

* Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

2.2. Background

2.2.1. SARS-CoV-2

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.[10,11] Therefore, vaccines targeting the spike protein of SARS-CoV-2 have been used as a critical mitigation strategy of the COVID-19 pandemic. However, waning effectiveness of the authorized vaccines has been shown to occur over time and is suspected to be due to waning of vaccine-induced immunity as well as the emergence of VOCs.

2.2.2. Influenza

Influenza is a major cause of morbidity and mortality worldwide, occurring in annual seasonal epidemics and occasionally in global pandemics.[12] Symptomatic influenza infection causes a febrile illness with respiratory and systemic symptoms,[13] although it may often be asymptomatic.[14] 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, an average of >200,000 hospitalizations per year are related to influenza,[15] while the annual global number of deaths is estimated to range from almost 300,000 to over 600,000.[16]

Influenza viruses are part of the *Orthomyxoviridae* family and are divided into 3 genera or types (A, B, and C) based upon antigenic differences in the nucleoprotein and the matrix protein. Influenza A viruses are further classified into subtypes based upon the membrane glycoproteins, HA and NA.[17] The RNA genome is segmented, which allows genetic reassortment among viruses of the same type.[17] This genetic instability can result in the phenomenon known as antigenic shift, involving a major change in 1 or both of the HAs and NAs, which, if efficiently transmissible, can result in a pandemic. More common are multiple point mutations in the genome, leading to more minor changes in the HA and NA, known as antigenic drift.[15] This genetic instability is what necessitates vaccines that are tailored annually.[15]

2.2.3. Clinical Overview

2.2.3.1. SARS-CoV-2

Study C4591001 (NCT04368728) is an ongoing Phase 1/2/3 trial in ~46,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from a novel RNA-based vaccine candidate.[18] The trial is being conducted in a heterogeneous study population: eligible participants ≥12 years of age, healthy participants, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants.

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 36,621 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.

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.[19] 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.[18]

On 22 September 2021, based on safety and immunogenicity data from approximately 300 immunocompetent adult booster dose recipients from Study C4591001, the FDA issued the EUA for a single booster dose of BNT162b2 30 µg for:

1. individuals 65 years of age and older;

2. individuals 18 through 64 years of age at high risk of severe COVID-19; and

3. individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19, including severe COVID-19.[20]

On 19 November 2021, the FDA amended the EUA, authorizing use of a single booster dose for all individuals 18 years of age and older after completion of primary vaccination with an FDA-approved COVID-19 vaccine.[21] On 09 December 2021, the FDA again amended the EUA to authorize the use of a single booster dose for administration to individuals 16 and 17 years of age at least 6 months after completion of primary vaccination with BNT162b2. In addition, a booster dose of the vaccine is authorized in the EU and other countries, with recommendations for populations varying based on local health authority guidance.

C4591031 Substudy E is an ongoing Phase 3 trial in approximately 2900 participants 18 years of age and older who have previously received 3 doses of BNT162b2 (30-µg dose). Participants in this substudy received a fourth dose of either BNT162b2 or BNT162b2 Omicron (BA.1 sublineage) or a combination of both at a total dose level of either 30 µg or 60 µg. From the available safety data from this study, the tolerability and safety profile of bivalent BNT162b2 30 µg, bivalent BNT162b2 60 µg, and monovalent BNT162b2 60 µg up to 1 month after study vaccination (to the data cutoff date) was acceptable and consistent with the known safety profile of BNT162b2 and the previously reported AE profile for Omicron BA.1–modified BNT162b2 vaccines. In participants >18 through 55 years of age, monovalent and bivalent Omicron-modified vaccines at the 30-µg dose level showed a similar local reaction and systemic event profile as the prototype BNT162b2. In the older age group at the 60-µg dose level, mild to moderate injection site pain, fatigue, and muscle pain were more common compared to the reactogenicity with the 30-µg dose level. From the immunogenicity data, in participants >55 years of age without evidence of COVID-19 infection, Omicron BA.1 neutralization activity substantially increased with Omicron-modified bivalent vaccines as a fourth dose. Additionally, analysis of immunogenicity data from this study demonstrated a robust Omicron BA.1 and reference-strain vaccine-elicited immune response to both monovalent and bivalent Omicron BA.1–modified vaccines when administered as a fourth dose to BNT162b2-experienced participants 18 through 55 years of age.

Considering the waning effectiveness of the primary series of BNT162b2 as well as 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 could generate improved immune responses against the variants has become imperative, as this could help better protect individuals against COVID-19. This need has been reemphasized by the FDA since June 2022 when it called for trials with modified vaccines containing an Omicron BA.4/BA.5 component at emergence of that strain.[22]

Related to this series of developments is the C4591044 study (NCT05472038). This is an ongoing Phase 2/3, randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new bivalent variant vaccines at the standard or higher dose. The study evaluates bivalent BNT162b2 (original/Omi BA.4/BA.5) given as a fourth dose in participants 12 through 17, 18 through 55, and >55 years of age. Preliminary data demonstrated that the safety profile within 1 month after vaccination (Dose 4) with bivalent BNT162b2 (original/Omi BA.4/BA.5) at the 30-µg dose level was favorable across all age groups, with mostly mild or moderate reactogenicity, and few participants reported AEs. Analysis of immunogenicity data at 1 month after vaccination in the evaluable immunogenicity population with or without evidence of infection up to 1 month after study vaccination for BNT162b2-experienced participants 18 through 55 years and >55 years of age who received a fourth dose with bivalent BNT162b2 (original/Omi BA.4/BA.5) 30 µg demonstrated a robust vaccine-elicited immune response. Superiority of bivalent BNT162b2 (original/Omi BA.4/BA.5) 30 µg to BNT162b2 30 µg in the >55-year age group from C4591031 Substudy E with respect to anti–Omicron BA.4/BA.5 neutralizing titers was met. Noninferiority based on seroresponse for bivalent BNT162b2 (original/Omi BA.4/BA.5) 30 µg to BNT162b2 30 µg in the >55-year age group was also met. Additionally, noninferiority of anti–reference-strain immune response based on the GMR of bivalent BNT162b2 (original/Omi BA.4/BA.5) 30 µg to BNT162b2 30 µg in the >55-year age group was met. The results suggest an anticipated improved clinical benefit against COVID-19 due to Omicron BA.4/BA.5 with bivalent BNT162b2 (original/Omi BA.4/BA.5) compared to BNT162b2 as a fourth dose.

2.2.3.2. Influenza

Influenza modRNA has been evaluated in 2 Pfizer-sponsored clinical trials: C4781001 and C4781004.

C4781001: This is a Phase 1/2 study conducted from first participant first visit (September 2021) to last participant last visit (January 2023). The study evaluated monovalent, bivalent, and quadrivalent influenza vaccines in healthy adults 18 through 85 years of age. The final study report is pending.

The study evaluated monovalent RNA encoding influenza strains in doses up to [CCI] µg, bivalent RNA encoding 2 influenza strains in doses up to [CCI] µg/strain (= [CCI] µg total RNA dose), quadrivalent RNA encoding 4 influenza strains in doses up to [CCI] µg/strain (= [CCI] µg total RNA dose), and combinations of monovalent and bivalent RNA vaccines given concomitantly or staggered with licensed influenza vaccines.

The data gathered to date in this study have demonstrated that a single dose of qIRV (CCI µg or CCI µg) was well tolerated and elicited immune responses against influenza in participants 18 through 85 years of age. Together, these data supported progression to Phase 3 clinical development of qIRV (CCI µg) for adults ≥65 years of age and qIRV (CCI µg) for adults 18 through 64 years of age. Based on immunogenicity data observed in Study C4781001, Phase 3 Study C4781004 was designed to evaluate the efficacy and immunogenicity to determine effectiveness, along with safety analyses to assess tolerability and risk, of qIRV when administered to a large cohort of adults at the age group–selected dose levels.

C4781004: A Phase 3 study that initiated dosing in adults 18 years of age and older in September 2022. The study is ongoing and has dosed an estimated 53,200 adults across the northern and southern hemispheres. The study is evaluating doses of CCI µg and CCI µg quadrivalent modRNA influenza vaccines in adults 18 through 64 years of age and ≥65 years of age, respectively. Based on the randomization scheme, this reflects a safety database of over CCI participants in each age cohort who have received a dose of modRNA influenza vaccine at each dose level. Ongoing review of safety data from this study by an independent DMC has endorsed continued study enrollment.

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

The latest safety and immunogenicity results can be found in the IB for qIRV.

The rationale for the dose level selected for each study intervention used in this study is provided in Section 4.3.

2.2.3.3. Combined Influenza and COVID-19 Vaccines

As reflected in other sections of this document, both SARS-CoV-2 and influenza continue to cause significant healthcare burden due to global circulation.[4,12] Vaccination remains an important means of reducing the risk of significant morbidity and mortality.[15] Coadministration of vaccines against both of these pathogens could provide significant advantages to both patients and caregivers in terms of simplifying care. This clinical development program is intended to determine if 2 modified modRNA vaccines designed to target influenza and the SARS-CoV-2 virus can demonstrate an acceptable safety and immunogenicity profile.

The different vaccine groups to be evaluated in this clinical trial will determine the immunogenicity and safety profile of different doses of the influenza and SARS-CoV-2 antigens, of different methods of vaccine combination CCI [redacted] The summary of these groups is included in Table 2.

2.3. Benefit/Risk Assessment

The available safety and immunogenicity data from ongoing clinical trials and real-world effectiveness and safety data for BNT162b2, combined with available nonclinical data with BNT162 vaccines, as well as data from nonclinical and clinical trials with qIRV, support a favorable benefit/risk profile and support clinical development of a vaccine combining these components. Taking into account the measures to minimize risk to study participants, the potential risks identified in association with the study intervention are justified by the anticipated benefits that may be afforded to healthy participants.

Clinical investigation is justified, given:

- The threat posed by continuous new outbreaks of SARS-CoV-2 infections worldwide.
- The threat posed by the SARS-CoV-2 variants emerging worldwide.
- The potential need for enhancing immune responses to overcome waning immunity.
- The potential advantages and convenience to individuals in developing a combined vaccine against SARS-CoV-2 and influenza that would align with the recent FDA recommendations for an annual COVID-19 vaccination approach, similar to that for influenza.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of IRV (qIRV, bIRV, or tIRV)/BNT162b2 (original/Omi BA.4/BA.5), IRV, and BNT162b2 may be found in the IBs, respectively, which are the SRSDs for this study. The SRSD for Substudy A is the licensed Fluzone SD USPI, and the SRSD for Substudy B is the licensed Flucelvax USPI.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): IRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5), IRV, and BNT162b2 Omicron (BA.4/BA.5)		
For IRV:		
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,[23] as well as the COVID-19 vaccine BNT162b2, which is also based on modRNA. The most common events reported in a large-scale efficacy study with BNT162b2 (C4591001) were mild to moderate pain at the injection site, fatigue, and headache.[18] 1-Week follow-up reactogenicity data of 194 participants who received mIRV, bIRV, or qIRV in C4781001 Substudy A	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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and 120 participants from C4781001 Substudy B showed most events to be mild to moderate in severity, with the most common events being pain at the injection site, fatigue, and headache.	All study participants will be observed for at least 30 minutes after vaccination.
The safety profile of a novel vaccine is not yet fully characterized.	Although IRVs are novel vaccines, they are based on the same platform (modRNA) as the COVID-19 vaccine BNT162b2, which has been shown to have a positive benefit/risk profile.	AE and SAE reports will be collected from the signing of the ICD through 4 weeks and 6 months after vaccination (for all substudies). All participants will be observed for at least 30 minutes after vaccination.
For BNT162b2 Omicron (BA.4/BA.5)		
This vaccine has the same modRNA platform (with sequence changes limited to those that are Omicron-specific) and LNP formulation as 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.[18] 1-Week follow-up reactogenicity data of 194 participants who received mIRV, bIRV, or qIRV in C4781001 Substudy A and 120 participants from C4781001 Substudy B showed most events to be mild to moderate in severity, with the most common events being pain at the injection site, fatigue, and headache. 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	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. Collection of AEs from the signing of the ICD through 4 weeks after vaccination, and SAEs through 6 months after Visit 1/201. 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 10.11.8.8.10 and Section 10.12.8.12.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	
Study Intervention(s): QIV–Fluzone SD and QIV–Flucelvax		
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, new or worsened muscle pain, new or worsened joint pain, Guillain-Barré syndrome, and syncope) following vaccination.	These are common adverse reactions seen with other vaccines.[24,25,26]	The study employs the use of a reactogenicity e-diary after vaccination, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol. All study participants will be observed for at least 30 minutes after vaccination.
Study Procedures		
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants enrolled in Substudy A are detailed in Section 10.11.2.3.

Benefits to individual participants enrolled in Substudy B are detailed in Section 10.12.2.3.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants as stated in Section 2.3.1, the potential risks identified in association with all active study interventions are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

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

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

4. STUDY DESIGN

4.1. Overall Design

See Section 10.11.4 for the Substudy A design.

See Section 10.12.4 for the Substudy B design.

4.2. Scientific Rationale for Study Design

See Section 2.1.

4.2.1. Diversity of Study Population

See Section 5.

4.2.2. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for the modRNA influenza vaccines used in this study, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. The use of a highly effective method of contraception is required for sexual intercourse involving a WOCBP (see Section 10.5).

4.3. Justification for Dose

4.3.1. Bivalent BNT162b2 (Original/Omi BA.4/BA.5)

Based on data from the Phase 1 component of clinical trial C4591001 and available nonclinical data, the modRNA BNT162b2 vaccine candidate was selected at a dose of 30 µg for Phase 2 and 3 evaluation of safety, immunogenicity, and efficacy after 2 doses administered 3 weeks apart. This is the dose that was shown to be effective and has been approved in multiple countries worldwide.

In November 2021, the FDA issued an EUA for a single booster dose of bivalent BNT162b2 (original/Omi BA.4/BA.5) at a dose level of 30 µg (15 µg original BNT162b2 and 15 µg BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5]) in individuals ≥18 years of age, and this dose level is being used in this study when bivalent BNT162b2 (original/Omi BA.4/BA.5) is administered alone.[27]

4.3.2. qIRV

Preliminary results among 45 participants in Study C4781001 exposed to either [CCI] µg or [CCI] µg qIRV noted that the combination is well tolerated with mainly mild to moderate local reactions and systemic events consistent with rates observed with BNT162b2. Based on Phase 2 safety and immunogenicity data, the dose level of qIRV being studied in the Phase 3 C4781004 protocol by age stratum is [CCI] µg for participants 18 through 64 years of age and [CCI] µg for participants ≥65 years of age.

Hence, doses of [CCI] µg and [CCI] µg qIRV, in addition to a midpoint dose of [CCI] µg qIRV, will be evaluated in Substudies A and B when administered alone or in combination with bivalent BNT162b2 (original/Omi BA.4/BA.5).

4.3.3. qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5)

qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combinations not exceeding [CCI] µg will be evaluated in Substudies A and B.

In Substudy A, dose-level combinations 1 through 3 as shown in Table 1 will be evaluated. Substudy B will evaluate various dose-level combinations in participants 18 through 64 years of age (Table 2) (as detailed in Section 10.12.4.1). These dose-level combinations in Substudy B were [CCI]

Based on Phase 2 C4781004 safety and immunogenicity data, the dose level of qIRV being studied in the Phase 3 C4781004 study, by age stratum, is [CCI] µg for participants 18 through 64 years of age and [CCI] µg for participants ≥65 years of age; hence, the corresponding dose level will be used in qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) administered during Substudy B to participants 18 through 64 years of age. Based on preliminary data from Substudy A, Substudy B will study additional combinations of COVID-19/influenza modRNA. This is supported by an acceptable tolerability profile for a dose up to [CCI] µg of a combination of influenza modRNA and COVID-19 modRNA, with opportunity to increase the immune response against both COVID-19 and influenza strains.

4.3.4. tIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5)

tIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combinations not exceeding [CCI] µg will be evaluated in this study as exploratory objectives, based on immunogenicity data from Substudy A and Substudy B.

Based on preliminary data from Substudy A, Substudy B will study a different combination of COVID-19/influenza modRNA vaccine in the form of tIRV: [redacted] µg ([redacted], and [redacted] and [redacted] µg bivalent BNT162b2 (original/Omi BA.4/BA.5). This is supported by an acceptable tolerability profile for a dose up to [redacted] µg of a combination of influenza modRNA and COVID-19 modRNA, with opportunity to increase the immune response against both COVID-19 and influenza strains.

4.3.5. bIRV/Bivalent BNT162b2

bIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combinations not exceeding [redacted] µg will be evaluated in Substudy B as exploratory objectives, based on immunogenicity data from Substudy A.

Based on preliminary data from Substudy A, Substudy B will study a different combination of COVID-19/influenza modRNA vaccine in the form of bIRV given concurrently with QIV in the opposite arm: [redacted] µg ([redacted] and [redacted] µg bivalent BNT162b2 (original/Omi BA.4/BA.5). This is supported by an acceptable tolerability profile for a dose up to [redacted] µg maximum and opportunity to increase the immune response.

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 Substudy B.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last visit.

5. STUDY POPULATION

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

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

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

5.1. Inclusion Criteria

See Section 10.11.5.1 for the Substudy A inclusion criteria.

See Section 10.12.5.1 for the Substudy B inclusion criteria.

5.2. Exclusion Criteria

See Section 10.11.5.2 for the Substudy A exclusion criteria.

See Section 10.12.5.2 for the Substudy B exclusion criteria.

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 5, Section 10.5.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoAs, the investigator or designee will inform the participant of the need to use acceptable effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

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

5.4. Screen Failures

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

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

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

See Section 10.11.5.3 for temporary delay criteria for Substudy A.

See Section 10.12.5.3 for temporary delay criteria for Substudy B.

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.

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

- qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5), which is a combination of the following, administered at the dose-level combinations shown in Table 1 for Substudy A and Table 2 for Substudy B.
  - qIRV encoding HA of 4 strains as seasonally recommended for the influenza season (CCI) or CCI, with the strain combinations as shown in Table 1 for Substudy A and Table 2 for Substudy B.
  - Bivalent BNT162b2 (original/Omi BA.4/BA.5), which contains original BNT162b2 and BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5), at a dose of either:
    - CCI µg, ie, CCI µg of original BNT162b2 and CCI µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5), or
    - CCI µg, ie, CCI µg of original BNT162b2 and CCI µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)
- tIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5), which is a combination of the following, administered at the dose-level combinations shown in Table 2:
  - CCI µg tIRV encoding HA of 3 strains as seasonally recommended for the influenza season (CCI and CCI)
  - CCI µg Bivalent BNT162b2 (original/Omi BA.4/BA.5), which contains original BNT162b2 and BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)
- bIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5), which is a combination of the following, administered at the dose-level combinations shown in Table 2:
  - CCI µg bIRV encoding HA of CCI as seasonally recommended for the influenza season CCI)

  - [redacted]µg Bivalent BNT162b2 (original/Omi BA.4/BA.5), which contains original BNT162b2 and BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)

- [redacted]µg qIRV, ie, encoding HA of 4 strains as seasonally recommended for the influenza season [redacted]
- [redacted]µg qIRV, ie, encoding HA of 4 strains as seasonally recommended for the influenza season [redacted]
- Licensed QIV

Table 3 describes the vaccine details for each of the constituent parts of the study interventions.

Table 1. Substudy A: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations

Substudy A Vaccine Group	qIRV Dose	Bivalent BNT162b2 (Original*/Omi BA.4/BA.5) Dose	Total modRNA Dose
1	[redacted]µg, ie, [redacted]	[redacted]µg, ie, • [redacted]µg of original BNT162b2 and • [redacted]µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)	[redacted]µg
2	[redacted]µg, ie, [redacted]	[redacted]µg, ie, • [redacted]µg of original BNT162b2 and • [redacted]µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)	[redacted]µg
3	[redacted]µg, ie, [redacted]	[redacted]µg, ie, • [redacted]µg of original BNT162b2 and • [redacted]µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)	[redacted]µg

Table 2. Substudy B: All Vaccine Groups

Substudy B Vaccine Group	qIRV/Bivalent BNT162b2 Dose-Level Combinations[a]	qIRV, tIRV, or bIRV	Bivalent BNT162b2[b]	Licensed QIV	LNP Dose	Total modRNA Dose	Approximate Number of Participants
1	N/A	N/A	CCI µg	Licensed QIV	CCI mg	CCI µg	30
2[c]	N/A	CCI µg bIRV (CCI	µg	Licensed QIV	mg	µg	30
3	1	CCI µg qIRV (CCI)	µg	N/A	mg	µg	120
4[d]	2	CCI µg qIRV CCI (CCI)	µg CCI	N/A	mg	µg	120
5	3	CCI µg qIRV (CCI)	CCI µg	N/A	mg	µg	120
6	4	CCI µg qIRV (CCI)	µg	N/A	mg	µg	30
7	5	CCI µg qIRV (CCI)	µg	N/A	mg	µg	30
8	6	CCI µg qIRV (CCI)	µg	N/A	mg	µg	30
9	7	CCI µg qIRV (CCI)	µg	N/A	mg	µg	30
10	8	CCI µg qIRV (CCI)	µg	N/A	mg	µg	30

Table 2. Substudy B: All Vaccine Groups

Substudy B Vaccine Group	qIRV/Bivalent BNT162b2 Dose-Level Combinations[a]	qIRV, tIRV, or bIRV	Bivalent BNT162b2[b]	Licensed QIV	LNP Dose	Total modRNA Dose	Approximate Number of Participants
11[c]	N/A	CCI µg tIRV (CCI)	CCI µg	N/A	CCI mg	CCI µg	30
12[d]	N/A	qIRV CCI	N/A	N/A	mg	µg	30

a. For qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) that CCI mIRVs encoding HA for each A and B strain will be CCI to generate qIRV at the dose-level combination shown; the resultant qIRV will then be CCI with bivalent BNT162b2 (original/Omi BA.4/BA.5) prior to administration. Please see the IPM for further details.

b. For bivalent BNT162b2 formulations: CCI µg total dose includes CCI µg of Omicron BA.4/BA.5 and CCI µg of the ancestral SARS-CoV-2 strain; CCI µg total dose includes CCI µg of Omicron BA.4/BA.5 and CCI µg of the ancestral SARS-CoV-2 strain. Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

c. Groups 2 and 11: bIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) and tIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) are CCI

d. Groups 4 and 12: qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) and qIRV are CCI

Note: The following influenza strains are included in the IRV in each group at the dose level noted:
Group CCI
Groups CCI through CCI and CCI CCI
Group CCI
Group

Table 3. Substudy A and Substudy B: Vaccine Details

Vaccine Preparation	Vaccine Antigen	Strain
PF-07829855 Influenza modRNA Suspension for Injection, 0.1 mg/mL	CCI [redacted]	Influenza A
PF-07966731 Influenza modRNA Suspension for Injection, 0.1 mg/mL		Influenza A
PF-07836258 Influenza modRNA Suspension for Injection, 0.1 mg/mL		Influenza A
PF-07871853 Influenza modRNA Suspension for Injection, 0.1 mg/mL		Influenza A
PF-07872963 Influenza modRNA Suspension for Injection, 0.1 mg/mL		Influenza B
PF-07836259 Influenza modRNA Suspension for Injection, 0.1 mg/mL		Influenza B
PF-07871992 Quadrivalent Influenza modRNA Suspension for Injection, 0.06 mg/mL[b]	2022/2023 northern hemisphere, C µg dose	CCI [redacted]
PF-07871992 Quadrivalent Influenza modRNA Suspension for Injection, 0.12 mg/mL[b]	2022/2023 northern hemisphere CC µg dose	
BNT162b2 bivalent [WT and Omicron (BA.4/BA.5) variant] 100 µg/mL	2022/2023 northern hemisphere COVID-19	COVID-19

a. This A strain will be updated to CCI [redacted] based on the 2023-2024 northern hemisphere seasonal influenza strain selection in Substudy B.
b. CCI [redacted]

6.1. Study Intervention(s) Administered

See Section 10.11.6.1 for study interventions to be administered during Substudy A.

See Section 10.12.6.1 for study interventions to be administered during Substudy B.

6.1.1. Administration

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

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

Study intervention administration details will be recorded on the CRF.

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

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

6.1.2. Medical Devices

QIV may be provided as PFSs and, in which case, should be considered a medical device.

All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.8) 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 prepared study intervention.

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

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

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

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

6.2.1. Preparation and Dispensing

See the IPM for instructions on how to prepare the study intervention for administration. Study intervention should be prepared, verified, 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 (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) will verify the dispensing.

See Section 10.11.6.1.3.1 for further details regarding preparation and dispensing for Substudy A.

See Section 10.12.6.1.3.1 for further details regarding preparation and dispensing for Substudy B.

6.3. Assignment to Study Intervention

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

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

6.4. Blinding

See Section 10.11.6.2 for Substudy A blinding arrangements.

See Section 10.12.6.2 for Substudy B blinding arrangements.

6.4.1. Blinding of Participants

Substudy A blinding arrangements for participants are detailed in Section 10.11.6.2.1.

Substudy B blinding arrangements for participants are detailed in Section 10.12.6.2.1.

6.4.2. Blinding of Site Personnel

Substudy A blinding arrangements for site personnel are detailed in Section 10.11.6.2.2.

Substudy B blinding arrangements for site personnel are detailed in Section 10.12.6.2.2.

6.4.3. Blinding of the Sponsor

Substudy A blinding arrangements for the sponsor are detailed in Section 10.11.6.2.3.

Substudy B blinding arrangements for the sponsor are detailed in Section 10.12.6.2.3.

6.4.4. Breaking the Blind

See Section 10.11.6.2.4 for details on blind-breaking procedures for Substudy A.

See Section 10.12.6.2.4 for details on blind-breaking procedures for Substudy B.

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 and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.

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

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

6.9. Prior and Concomitant Therapy

See Section 10.11.6.7 for Substudy A prior and concomitant therapy.

See Section 10.12.6.7 for Substudy B prior and concomitant therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

7.2. 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 vaccine outside of the study-specified time points). See Section 10.11 for Substudy A and Section 10.12 for Substudy B.

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) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

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

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

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

8.2. Efficacy and/or Immunogenicity Assessments

See Section 10.11.8.1 for Substudy A immunogenicity assessments.

See Section 10.12.8.3 for Substudy B immunogenicity assessments.

8.2.1. Biological Samples

Blood and midturbinate swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory analyst testing the samples will not know the participant's identity, study visit, or study cohort associated with the sample. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the

ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other vaccines or vaccine-related products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

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

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

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

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

Safety parameters also include reactogenicity e-diary reports of local reactions, systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.3.5.

8.3.1. Physical Examinations

In Substudy A, a physical examination will be performed at the screening visit and, if clinically indicated, prior to the participant's first vaccination (at Visit 1 in Substudy A). In Substudy B, a physical examination will be performed at the screening visit and, if clinically indicated, prior to the participant's first vaccination (at Visit 201).

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

8.3.2. Vital Signs

For Substudy A, the participant's oral temperature, pulse rate, and seated blood pressure will be measured at screening, prior to vaccination at Visit 1, Visit 2, and Visit 3. Additionally, weight and height will be measured at screening.

For Substudy B, the participant's oral temperature, pulse rate, and seated blood pressure will be measured at screening, prior to vaccination at Visit 201, at Visit 202, and at Visit 203. Additionally, weight and height will be measured at screening.

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. Electrocardiograms

See Section 10.11.8.4.1 for Substudy A ECG requirements.

See Section 10.12.8.5.1 for Substudy B ECG requirements.

8.3.4. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will be conducted in Substudy A and Substudy B.

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

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

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

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

See Section 10.6 for suggested actions and follow-up assessments in the event of potential DILI.

See Section 10.7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.5. Electronic Diary

All participants will be required to complete a reactogenicity e-diary after each vaccination given at Visits 1 and 201 through an application installed on a provisioned device or on the participant's own personal device. All participants will be asked to monitor and record local reactions, systemic events, and use of antipyretic medication for 7 days from the day of administration of the study intervention given at Visits 1 and 201. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF, unless the participant missed an e-diary entry and the participant experienced a prompted local reaction or systemic event, in which case any missed entries should be included in the AE CRF.

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

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

8.3.5.1. 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.[23]

8.3.5.2. Local Reactions

Following vaccination (where Day 1 is the day of vaccination), participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary daily. **In Substudies A and B, local reactions will be assessed at the injection site on the right arm only after vaccinations given at Visits 1 and 201.**

If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. 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
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

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

Table 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
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

8.3.5.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily for 7 days 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.

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)

8.3.5.5. Antipyretic Medication

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

8.3.6. Pregnancy Testing

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

Substudy A

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 4 (4-week follow-up visit). Additionally, any AEs occurring up to 48 hours after the blood draws at Visits 4 and 5 must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the participant's last study vaccination (Visit 6).

Substudy B

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 204. Additionally, any AEs occurring up to 48 hours after the blood draws at Visit 204 in Substudy B (if eligible as per Section 10.12.1) must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the participant's first study vaccination (Visit 205).

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the Vaccine SAE Report Form 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 on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the study intervention.

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

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

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

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

8.4.7. Adverse Events of Special Interest

The following events are considered AESIs:

For Substudy A:

- A confirmed diagnosis of influenza.
- Confirmed diagnosis of myocarditis or pericarditis occurring within 4 weeks after vaccination. See Section 10.11.8.8.10.
- Confirmed COVID-19 diagnosis after Visit 1 through the end of the study (clinical signs/symptoms per CDC[28] and positive SARS-CoV-2 NAAT or rapid antigen test result).

For Substudy B:

- A confirmed diagnosis of influenza.
- Confirmed diagnosis of myocarditis or pericarditis occurring within 6 weeks after vaccination. See Section 10.12.8.12.
- Confirmed COVID-19 diagnosis after Visit 201 through the end of the study (clinical signs/symptoms per CDC[28] and positive SARS-CoV-2 NAAT or rapid antigen test result) (excluding Group 12).
- Potential menstrual cycle disturbances. See Section 10.12.8.11.

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

8.4.7.1. 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**.

8.4.8. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.1.2.

In order to fulfill regulatory reporting obligations worldwide, the unblinded site staff is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.10.

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 8.4.4and Section 10.3 of the protocol.

8.4.8.1. 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 10.10.4 for instructions for documenting and reporting medical device deficiencies.

8.4.8.2. Regulatory Reporting 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.

8.4.9. Vaccination Errors

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

Vaccination errors are recorded and reported as follows:

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

Vaccination errors include:

- Vaccination errors involving participant exposure to the study intervention;

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

- The administration of expired study intervention;

- The administration of an incorrect study intervention;

- The administration of an incorrect dosage;

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

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

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

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

8.6.1. Specified Genetics

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

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

See Section 10.11.8.1 for Substudy A.

See Section 10.12.8.3 for Substudy B.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in Substudy A or Substudy B.

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 are no statistical hypotheses in either Substudy A or Substudy B.

9.1.1. Estimands

Refer to Section 10.11.9.1.1 for the estimands in Substudy A.

Refer to Section 10.12.9.1.1 for the estimands in Substudy B.

9.1.2. Multiplicity Adjustment

Refer to Section 10.11.9.1.2 for multiplicity adjustment in Substudy A.

Refer to Section 10.12.9.1.2 for multiplicity adjustments in Substudy B.

9.2. Analysis Sets

Refer to Section 10.11.9.2 for analysis sets in Substudy A.

Refer to Section 10.12.9.2 for analysis sets in Substudy B.

9.3. Statistical Analyses

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

Statistical analyses for Substudy A are detailed in Section 10.11.9.3.

Statistical analyses for Substudy B are detailed in Section 10.12.9.3.

9.3.1. General Considerations

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

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Completely missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules. Missing e-diary data not recorded in the e-diary will be recorded on the AE CRF. Therefore, the primary analysis will use reactogenicity recorded as AEs in the CRF to impute the missing e-diary data.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. Antibody titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for immunogenicity analysis. No other missing assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ.

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

9.3.1.1. Analyses for Binary Data

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

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

9.3.1.2. Analyses for Continuous Data

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

9.3.1.2.1. Geometric Mean Titers

The GMTs will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale.

Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to the Student t distribution, and then exponentiating the confidence limits.

9.3.1.2.2. Geometric Mean Fold Rises

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

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.2.3. Reverse Cumulative Distribution Curves

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

9.4. Interim Analyses

Details for interim analyses will be provided in Section 10.11.9.4 for Substudy A and Section 10.12.9.4 for Substudy B.

9.5. Sample Size Determination

Refer to Section 10.11.9.5 for sample size determination related to Substudy A.

Refer to Section 10.12.9.6 for sample size determination related to Substudy B.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

10.1.3.1. 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 ICD (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

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

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

The responsibilities of the IRC will include at a minimum:

- Review of safety data in the case of a stopping rule being met in Substudy A and Substudy B.
- Review of safety data and immunogenicity accumulated for at least 4 weeks following vaccination in Substudy A and Substudy B.

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.

<u>EudraCT/CTIS</u>

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.8. Source Documents

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

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

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

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

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

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

10.1.9. Study and Site Start and Closure

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

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

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

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

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

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

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

10.1.10. Publication Policy

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

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

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

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

10.1.11. Sponsor's Medically Qualified Individual

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory test will be performed at times defined in Section 10.11.1 for Substudy A and Section 10.12.1 for Substudy B of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Investigators must document their review of each laboratory safety report.

Substudy A and Substudy B	
Hematology	**Chemistry**
N/A	Cardiac troponin I

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

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

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

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

10.3.2. Definition of an SAE

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

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE 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.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

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

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

10.3.4. Reporting of SAEs

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

SAE Reporting to Pfizer Safety via the Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE 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: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention and susceptibility to and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis. Influenza strain sequencing of LCI cases and SARS-CoV-2 strain sequencing of confirmed COVID-19 cases using next-generation sequencing technology may also be conducted from the midturbinate swab samples collected.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision-making without being included in a study report.

- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

  - Samples for specified genetic analysis (see Section 8.6.1) will be stored for up to 15 years or other period as per local requirements.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. 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 woman of childbearing potential who is not currently pregnant.

    OR

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

10.5.2. 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 10.5.4 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 10.5.3).

  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.

10.5.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

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

10.5.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

Highly Effective Methods That Are User Dependent

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

Sexual Abstinence

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

Other Effective Methods

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

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

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

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

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

10.7.2. Age-Specific Kidney Function Calculation Recommendations

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

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

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

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

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

Known HIV infection

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

Known HCV infection

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

Known HBV infection

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

10.9. Appendix 9: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex >120 ms).
• New-onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

10.10. Appendix 10: 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).

10.10.1. 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.

10.10.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 3 (Section 10.3.2).
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

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

10.10.3. 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.

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

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the unblinded site staff to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The unblinded site staff will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice. • If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF. • The unblinded site staff will notify the sponsor study team by telephone or 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 unblinded site staff determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the unblinded site staff will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. All relevant details related to the role of the device in regard to the SAE must be included in the Vaccine SAE Report Form as outlined in 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 10.1.8 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- For device deficiencies, it is very important that the unblinded site staff describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products in their assessment.

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

Follow-Up of Medical Device Deficiency

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form by the 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.

10.10.5. Reporting of SAEs

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

10.10.6. Reporting of SADEs

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

10.11. Appendix 11: Substudy A (Phase 1)

10.11.1. SoA – Substudy A (Phase 1)

Visit Number	Screening	1	2	3	4	5	6
Visit Description	Screening	Vaccination	Day 3 Follow-Up Visit	1-Week Follow-Up Visit	4-Week Follow-Up Visit	8-Week Follow-Up Visit	6-Month Telephone Contact
Visit Window (Days)	0 to 28 Days Before Visit 1	Day 1	2 to 4 Days After Visit 1	6 to 8 Days After Visit 1	26 to 30 Days After Visit 1	52 to 60 Days After Visit 1	175 to 189 Days After Visit 1
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data (including confirmed COVID-19 diagnosis or asymptomatic positive SARS-CoV-2 test result [NAAT or antigen test])	X						
Obtain details of medications currently taken	X						
Perform physical examination	X						
Perform clinical assessment[a]		X					
Measure height and weight	X						
Measure vital signs (including oral temperature)	X	X	X	X			
Perform 12-lead triplicate ECG	X	X	X	X			
Collect blood sample for troponin I laboratory testing	~2.5 mL	~2.5 mL[b]	~2.5 mL	~2.5 mL			
Urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X	X	X		
Collect prior COVID-19 and pneumococcal vaccine information	X						
Collect details of any licensed influenza vaccine received in the prior 12 months	X						
Collect nonstudy vaccine information	X	X	X	X	X	X	X
Collect prohibited medication use			X	X	X	X	X
Review troponin I and ECG results		X	X	X	X		
Confirm eligibility	X	X					
Obtain randomization number and study intervention allocation		X					
Nasal (midturbinate) swab for SARS-CoV-2 NAAT		X					
Collect blood sample for immunogenicity assessment		~50 mL[b]		~50 mL	~50 mL	~50 mL	
Administer study intervention		X					

Visit Number	Screening	1	2	3	4	5	6
Visit Description	**Screening**	**Vaccination**	**Day 3 Follow-Up Visit**	**1-Week Follow-Up Visit**	**4-Week Follow-Up Visit**	**8-Week Follow-Up Visit**	**6-Month Telephone Contact**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**2 to 4 Days After Visit 1**	**6 to 8 Days After Visit 1**	**26 to 30 Days After Visit 1**	**52 to 60 Days After Visit 1**	**175 to 189 Days After Visit 1**
Assess acute reactions for at least 30 minutes after study intervention administration		X					
Explain to the participant e-diary completion requirements and assist the participant with downloading the application or issue provisioned device if required		X					
Provide thermometer and measuring device		X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	—	—	—	→	
Review ongoing reactogenicity e-diary symptoms and obtain stop dates				X	X		
Collect AEs and SAEs as appropriate[c]	X	X	X	X	X	X	X
Collect e-diary or assist the participant with deleting application				X	X		

a. Including, if indicated, a physical examination.
b. Prior to vaccination at Visit 1.
c. AEs are collected from the completion of informed consent through Visit 4. SAEs are collected from the completion of informed consent through the end of study participation. Additionally, any AEs occurring up to 48 hours after blood draws at Visits 4 and 5 must be recorded.

10.11.2. Introduction for Substudy A

10.11.2.1. Substudy A Rationale

This is a Phase 1 randomized, open-label substudy to describe the safety and immunogenicity of up to 3 dose-level combinations of qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5).

10.11.2.2. Background for Substudy A

See Section 2.2.

10.11.2.3. Benefit/Risk Assessment for Substudy A

See Section 2.3.1 for overall study risks. No unique risks are identified for Substudy A.

Benefits to individual participants enrolled in Substudy A may be:

- Receipt of a dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey better protection against the SARS-CoV-2 WT (ancestral) strain and VOCs during a global pandemic.
- Receipt of a potentially efficacious influenza vaccine at no cost to the participant, and provision of the immunogenicity results in participants.
- Access to COVID-19 diagnostic testing.
- Contributing to research to help others in a time of global pandemic.

Please see Section 2.3 for details of the SRSDs relating to study intervention used in Substudy A.

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

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
To describe the safety and tolerability of qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at various dose-level combinations in participants ≥18 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately and combined, receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs from the first vaccination through 4 weeks after vaccination • SAEs from the first vaccination through 6 months after vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	The percentage of participants with: • Abnormal troponin I laboratory values 2 days and 1 week after vaccination	Troponin I laboratory parameters detailed in Section 10.2
	The percentage of participants with: • New ECG abnormalities 2 days and 1 week after vaccination	ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in Section 10.11.8.4.1
Secondary	**Secondary**	**Secondary**
To describe the immune responses elicited by qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at various dose-level combinations in participants ≥18 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately, complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 4 weeks after vaccination • GMFR from before vaccination to 4 weeks after vaccination • The proportion of participants achieving HAI seroconversion[a] for each strain at 4 weeks after vaccination • The percentage of participants with HAI titers ≥1:40 for each strain before vaccination and at 4 weeks after vaccination • The percentage of participants achieving HAI seroconversion for all strains at 4 weeks after vaccination • The percentage of participants with HAI titers ≥1:40 for all strains at 4 weeks after vaccination	HAI titers for the matched seasonal strains (CCI) recommended by WHO

Objectives	Estimands	Endpoints
	In participants 18 through 64 years of age and ≥65 years of age, separately, having received qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) and complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 4 weeks after vaccination for each strain • GMFR from before vaccination to 4 weeks after vaccination for each strain • Percentages of participants with seroresponse[b] at 4 weeks after vaccination for each strain	• SARS-CoV-2 Omicron BA.4/BA.5–neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
Exploratory	**Exploratory**	**Exploratory**
To describe the immune responses elicited by qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at various dose-level combinations in participants ≥18 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately, complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 1 and 8 weeks after vaccination • GMFR from before vaccination to 1 and 8 weeks after vaccination • The proportion of participants achieving HAI seroconversion[a] for each strain at 1 and 8 weeks after vaccination • The percentage of participants with HAI titers ≥1:40 for each strain before vaccination and at 1 and 8 weeks after vaccination • The percentage of participants achieving HAI seroconversion for all strains at 1 and 8 weeks after vaccination • The percentage of participants with HAI titers ≥1:40 for all strains at 1 and 8 weeks after vaccination	• HAI titers for the matched seasonal strains ([CCI] recommended by WHO
To describe the immune responses elicited by qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at various dose-level combinations in participants ≥18 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately, having received qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) and complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 1 and 8 weeks after vaccination for each strain • GMFR from before vaccination to 1 and 8 weeks after vaccination for each strain • Percentages of participants with seroresponse[b] at 1 and 8 weeks after vaccination for each strain	• SARS-CoV-2 Omicron BA.4/BA.5–neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers

Objectives	Estimands	Endpoints
To describe the immune response to emerging VOCs in participants ≥18 years of age		• SARS-CoV-2 neutralizing titers for VOCs not already specified

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

10.11.4. Substudy A Design

10.11.4.1. Overall Design for Substudy A

This is a Phase 1 randomized, open-label substudy to describe the safety and immunogenicity of up to 3 dose-level combinations of qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5). Bivalent BNT162b2 (original/Omi BA.4/BA.5) used was recommended by ACIP in 2022-2023.[29,30] Approximately 360 participants will be enrolled across 2 age strata: approximately 180 participants 18 through 64 years of age and approximately 180 participants ≥65 years of age. Participants in each stratum will be randomized equally (30 participants per group) to each group to receive a dose of either:

- qIRV/bivalent BNT162b2 (original*/Omi BA.4/BA.5), at 1 of the 3 dose-level combinations shown in Table 1,
- CCI µg qIRV,
- CCI µg qIRV, or
- CCI µg Bivalent BNT162b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to licensed QIV.

* Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Enrollment into each of the 2 age strata (18 through 64 and ≥65 years of age) may occur independently.

Safety and immunogenicity data from studies previously conducted in participants of a similar age range having received 1 dose of BNT162b2 at a dose level of CCI µg and CCI µg may be used as a control during the substudy analysis.

Enrollment in each age stratum will be controlled such that no more than 10 participants (considered the sentinel participants) can be vaccinated on the first day; vaccination of the remaining participants will commence no sooner than 24 hours after the tenth participant received his or her vaccination.

Stopping rules will apply to groups receiving combination bivalent BNT162b2 (original/Omi BA.4/BA.5) and qIRV as detailed in Section 10.11.8.6.

All participants will be asked to complete a reactogenicity e-diary for 7 days following each vaccination. Blood samples of approximately 50 mL will be collected for immunogenicity assessments prior to Vaccination 1 and at 1, 4, and 8 weeks after vaccination. All participants will be asked to provide an additional blood sample of approximately 2.5 mL at time points specified in Section 10.11.1 for assessment of troponin I.

Safety and immunogenicity data accumulated for at least 4 weeks following vaccination in each age stratum will be reviewed by the sponsor's IRC to determine if enrollment in each age stratum in Substudy B may proceed. Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, subsequent collection of blood samples from participants in that group may be halted and/or blood samples may not be analyzed, and study visits or other procedures may be discontinued.

The total duration of the study for each participant will be up to approximately 6 months.

10.11.4.2. Scientific Rationale for Study Design for Substudy A

See Section 2.1.

10.11.4.3. Justification for Dose for Substudy A

See Section 4.3.

10.11.4.4. End of Substudy Definition for Substudy A

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

A participant is considered to have completed the substudy if he/she has completed all periods of the substudy, including the last visit.

10.11.5. Substudy A Population

10.11.5.1. Substudy A Inclusion Criteria

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

Age and Sex:

1. Male or female participants ≥18 years of age (or the minimum age of consent in accordance with local regulations) at Visit 1 (Day 1).
    - Refer to Appendix 5 for reproductive criteria for male (Section 10.5.1) and female (Section 10.5.2) participants.

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

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

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

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.8.

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. **For participants 18 through 64 years of age:** participants who have received 3 prior doses of 30 µg BNT162b2, with the last dose being 150 days to 365 days before Visit 1 (Day 1).

   For participants ≥65 years of age: participants who have received 4 or 5 prior doses of a modRNA SARS-CoV-2 vaccine, with the last dose being a bivalent vaccine, 90 days to 365 days before Visit 1 (Day 1). Any fourth or fifth dose (booster dose) of modRNA SARS-CoV-2 vaccine received after 01 September 2022 may be considered to be a bivalent vaccine in the US.

Note: Documented confirmation of prior doses of modRNA SARS-CoV-2 vaccines received must be obtained prior to randomization.

6. **For participants ≥65 years of age:** receipt of licensed influenza vaccination for the 2022-2023 northern hemisphere season ≥120 days before study intervention administration.

10.11.5.2. Substudy A Exclusion Criteria

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

Medical Conditions:

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

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

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

4. Women who are pregnant or breastfeeding.

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

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

Prior/Concomitant Therapy:

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

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

9. **For participants 18 through 64 years of age:** vaccination with any investigational or licensed influenza vaccine within 6 months (175 days) before study intervention administration.

Prior/Concurrent Clinical Study Experience:

10. Participation in other studies involving a study intervention within 28 days before randomization. Anticipated participation in other studies within 28 days after receipt of study intervention in this study.

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

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

12. Participation in strenuous or endurance exercise through Visit 3.

13. Prior history of heart disease.

14. Any abnormal screening troponin I laboratory value.

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

10.11.5.3. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention for Substudy A

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

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

2. Current febrile illness (oral temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study intervention administration. This includes symptoms that could represent a potential COVID-19 illness (refer to Section 8.4.7).

   Note: The participant should be directed to seek additional testing through his/her primary healthcare provider at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing, as per local guidance.

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

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

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

10.11.6. Substudy A Intervention and Concomitant Therapy

10.11.6.1. Study Intervention(s) Administered for Substudy A

Study interventions for Substudy A will include:

Intervention Name	Bivalent BNT162b2 (original/Omi BA.4/BA.5) (original[a] BNT162b2 and BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5]) CCI	qIRV	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)	QIV
Arm Name (group of participants receiving a specific study intervention or no study intervention)	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) or Licensed QIV + bivalent BNT162b2 (original/Omi BA.4/BA.5)	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) or CCI µg qIRV or CCI µg qIRV	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)	Licensed QIV + bivalent BNT162b2 (original/Omi BA.4/BA.5)
Targeted Influenza Strains	N/A	For each season, strains as recommended by WHO for recombinant or cell-based influenza vaccines	For each season, strains as recommended by WHO for recombinant or cell-based influenza vaccines	For each season, strains as recommended by WHO
Type	Vaccine	Vaccine	Vaccine	Vaccine
Dose Formulation	modRNA	modRNA	modRNA	
Unit Dose Strength(s)	As detailed in the IPM	As detailed in the IPM	As detailed in the IPM	As detailed in the IPM
Dosage Level(s)	CCI µg or CCI µg (CCI µg original BNT162b2 and CCI µg BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5]) CCI µg original BNT162b2 and CCI µg BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5])	CCI µg (CCI CCI µg (CCI	Dose-level combination 1 as described in Table 1 CCI µg qIRV CCI µg (CCI BNT162b2 CCI µg (CCI µg original BNT162b2 and CCI µg BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5]) Dose-level combination 2 as described in Table 1	

			CCI µg qIRV CCI µg (CCI) BNT162b2 CCI µg (CCI µg original BNT162b2 and CCI µg BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5]) Dose-level combination 3 as described in Table 1 CCI µg qIRV CCI µg (CCI) BNT162b2 CCI µg (CCI µg original BNT162b2 and CCI µg BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5])	
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Comparator
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by Pfizer	Provided centrally by Pfizer	Study intervention will be generated by CCI at the dose-level combinations detailed above: • qIRV • Bivalent BNT162b2 (original/Omi BA.4/BA.5)	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.		Study intervention will be provided as either a PFS or a glass vial as open-label supply. Each vial will be labeled per country requirement.

a. Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Study Arms						
Group Number	1	2	3	4	5	6
Arm Title	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) Dose-level combination 1 as described in Table 1	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) Dose-level combination 2 as described in Table 1	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) Dose-level combination 3 as described in Table 1	CCI µg qIRV	CCI µg qIRV	Licensed QIV+ bivalent BNT162 b2 (original/ Omi BA.4/BA.5)
Arm Type	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants will receive qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 1 as described in Table 1	Participants will receive qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 2 as described in Table 1	Participants will receive qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 3 as described in Table 1	Participants will receive CCI µg of qIRV	Participants will receive CCI µg of qIRV	Participants will receive CCI µg of bivalent BNT162 b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to QIV
Associated Intervention Labels	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)	qIRV	qIRV	Bivalent BNT162b2 (original/Omi BA.4/BA.5) and QIV

10.11.6.1.1. Administration for Substudy A

See Section 6.1.1.

During Substudy A, participants will receive 1 dose of study intervention at Visit 1 in an open-label manner in accordance with the SoA (Section 10.11.1). Other than QIV, all study interventions for Substudy A should be administered intramuscularly into the deltoid muscle of the right arm; when QIV is coadministered with bivalent BNT162b2 (original/Omi BA.4/BA.5), QIV should be administered intramuscularly into the deltoid muscle of the left arm.

10.11.6.1.2. Medical Devices for Substudy A

See Section 6.1.2.

10.11.6.1.3. Preparation, Handling, Storage, and Accountability for Substudy A

See Section 6.2.

10.11.6.1.3.1. Preparation and Dispensing for Substudy A

See Section 6.2.1.

During Substudy A, study intervention will be prepared by qualified unblinded site personnel according to the IPM or package insert and the study intervention administered in an open-label manner.

10.11.6.1.4. Allocation to Study Intervention for Substudy A

See Section 6.3.

Allocation of study intervention at Visit 1 in Substudy A will be conducted via the IRT.

10.11.6.2. Blinding for Substudy A

10.11.6.2.1. Blinding of Participants for Substudy A

Participants will be unblinded to their assigned study intervention.

10.11.6.2.2. Blinding of Site Personnel for Substudy A

This study is an open-label substudy, such that all site personnel, including the investigator, investigator staff, and study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded.

10.11.6.2.3. Blinding of the Sponsor for Substudy A

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

10.11.6.2.4. Breaking the Blind for Substudy A

Not applicable.

10.11.6.3. Study Intervention Compliance for Substudy A

See Section 6.5.

10.11.6.4. Dose Modification for Substudy A

Not applicable.

10.11.6.5. Continued Access to Study Intervention After the End of the Study for Substudy A

See Section 6.7.

10.11.6.6. Treatment of Overdose for Substudy A

See Section 6.8.

10.11.6.7. Prior and Concomitant Therapy for Substudy A

For Substudy A, the following concomitant medications and vaccinations will be recorded in the CRF:

- Prior receipt of any COVID-19 vaccine.
- Prior receipt of any pneumococcal vaccine.
- Licensed influenza vaccine, if received during the 12 months prior to enrollment.
- Any vaccinations received from 28 days prior to study enrollment until the last visit (Visit 6).
- Prohibited medications listed in Section 10.11.6.7.1, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

10.11.6.7.1. Prohibited During the Study for Substudy A

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 28 days before and 28 days after study vaccination at Visit 1.
- Receipt of any other (nonstudy) coronavirus vaccine from enrollment through Visit 5 (8-week follow-up visit) is prohibited.
- Receipt of any other (nonstudy) seasonal influenza vaccine from enrollment through Visit 5 (8-week follow-up visit) is prohibited.
- Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study is prohibited.
- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment through 28 days after administration of the study intervention.
- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies, from 60 days before study intervention administration through conclusion of the study.

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

10.11.6.7.2. Permitted During the Study for Substudy A

- Medication other than that described as prohibited in Section 10.11.6.7.1 required for treatment of preexisting conditions or acute illness is permitted.

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

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

See Section 7.

10.11.8. Substudy A Assessments and Procedures

For Substudy A, the minimal blood sampling volume for all individual participants in this study is approximately 210 mL.

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

10.11.8.1. Immunogenicity Assessments for Substudy A

Samples will be collected at time points as specified in Section 10.11.1 from all participants, and the following assays run:

- HAI titers for the matched seasonal strains (CCI [redacted]) recommended by WHO

- SARS-CoV-2 neutralization assay (reference strain)

- SARS-CoV-2 neutralization assays (Omicron BA.4, Omicron BA.5; other VOCs of interest, including other Omicron sublineages, may also be evaluated)

10.11.8.2. N-Binding Antibody Test for Substudy A

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.

10.11.8.3. Biological Samples for Substudy A

See Section 8.2.1.

10.11.8.4. Safety Assessments for Substudy A

See Section 8.3.

Note, for Substudy A, local reactions will be assessed at the injection site on the right arm only (see Section 8.3.5).

10.11.8.4.1. ECGs for Substudy A

ECGs will be collected at the times specified in Section 10.11.1.

All scheduled 12-lead ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. The ECGs should be obtained **prior** to blood collection, measurement of blood pressure, and measurement of pulse rate. ECGs will be performed in triplicate.

ECG data will be submitted to a central laboratory for evaluation. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (see Section 10.3) and should be evaluated further, as clinically warranted.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that lead placement be in the same position each time during each assessment visit in order to achieve precise ECG recordings.

ECG abnormalities consistent with probable or possible myocarditis or pericarditis are those judged as such by a cardiologist, including:

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

Echocardiograms may be performed as detailed in Section 10.11.8.8.10.

ECG values of potential clinical concern are listed in Section 10.9.

10.11.8.5. Clinical Safety Laboratory Assessments for Substudy A

Please see Section 8.3.4. Additionally, see Section 10.2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

10.11.8.6. Stopping Rules for Substudy A

The following stopping rules are in place for participants in groups receiving combination bivalent BNT162b2 (original/Omi BA.4/BA.5) and qIRV **in Substudy A**, based on AE, ECG, and laboratory data review. These data will be reviewed 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 bivalent BNT162b2 (original/Omi BA.4/BA.5)/qIRV vaccine group(s) at the affected and, if applicable, higher total dose level CCI or CCI µg).
    - Study intervention administration may continue during the pause in vaccine groups receiving qIRV alone, or QIV administered concurrently with bivalent BNT162b2 (original/Omi BA.4/BA.5).
    - For all participants already vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur within 4 weeks after administration of bivalent BNT162b2 (original/Omi BA.4/BA.5)/qIRV. Each bivalent BNT162b2 (original/Omi BA.4/BA.5)/qIRV dose level will be evaluated for contribution to stopping rules independently.

Stopping Rule Criteria:

1. If any participant vaccinated develops:
    - A new ECG abnormality that a cardiologist judges consistent with probable or possible myocarditis or pericarditis, including:
        - Sustained atrial or ventricular arrhythmias
        - Second-degree Mobitz Type II or worse AV block, new bundle branch block
        - Diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis

- An abnormal troponin I value that is confirmed abnormal on repeat testing, assessed as related to study intervention by the investigator.

2. If ≥1 participant vaccinated develops confirmed myocarditis or pericarditis.

3. If any participant vaccinated dies.

4. ≥1 participant vaccinated experiences a Grade 4 unsolicited AE, or SAE of any severity, assessed as related by the investigator.

5. ≥2 participants vaccinated with bivalent BNT162b2 (original/Omi BA.4/BA.5)/qIRV at the same dose level 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 local reactions, systemic events, and fever specified in Section 8.3.5, 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.

10.11.8.7. Adverse Events, Serious Adverse Events, and Other Safety Reporting for Substudy A

See Section 8.4.

10.11.8.8. Study Procedures for Substudy A

10.11.8.8.1. Screening (0 to 28 Days Before Visit 1) for Substudy A

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 participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain medical history, including confirmed COVID-19 diagnosis (see Section 8.4.7) or asymptomatic positive SARS-CoV-2 test result (NAAT or antigen test), and any other medical history of clinical significance.
- Obtain details of any medications currently taken.

- Perform 12-lead triplicate ECG.
- Perform physical examination, including vital signs (weight, height, oral temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 8.3.4.
- Perform urine pregnancy test on WOCBP as described in Section 8.3.6.
- Discuss contraceptive use as described in Section 5.3.1.
- Record nonstudy vaccinations as described in Section 10.11.6.7.
- Review documentation of all prior COVID-19 vaccinations. All vaccines must be authorized for use in the US. Record prior receipt of any COVID-19 vaccine as described in Section 10.11.6.7.
- Record prior receipt of any pneumococcal vaccine as described in Section 10.11.6.7.
- Record details of any licensed influenza vaccine received in the prior 12 months, as described in Section 10.11.6.7.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.4.1.
- The investigator or an authorized designee completes the CRF.

10.11.8.8.2. Visit 1 – Vaccination (Day 1) for Substudy A

- It is anticipated that the procedures below will be conducted in a stepwise manner.
- Discuss contraceptive use as described in Section 5.3.1.
- Record nonstudy vaccinations as described in Section 10.11.6.7.
- Review screening laboratory results (troponin I) and ECG results.
- Perform 12-lead triplicate ECG.

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF or on the AE CRF as per Section 10.3.
- Measure vital signs, including oral temperature, pulse rate, and seated blood pressure.
- Perform urine pregnancy test on WOCBP as described in Section 8.3.6.
- Ensure that the participant continues to meet all of the inclusion criteria and none of the exclusion criteria.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system.
- On the day of and before vaccination, obtain a nasal (midturbinate) swab (collected by site staff).
- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 8.3.4.
- Collect a blood sample (approximately 50 mL), before administration of study intervention, for immunogenicity assessment.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle. Other than QIV, all study interventions for Substudy A should be administered intramuscularly into the deltoid muscle of the right arm; when QIV is coadministered with bivalent BNT162b2 (original/Omi BA.4/BA.5), QIV should be administered intramuscularly into the deltoid muscle of the left arm. Please refer to the IPM for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary completion requirement to the participant and assist the participant with downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

    - Severe pain at the injection site.

    - Any severe systemic event.

- Record AEs as described in Section 8.4.1.

- 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 immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.11.8.8.10).

- 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 updates the study intervention accountability records.

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

10.11.8.8.3. Visit 2 – Day 3 Follow-Up Visit (After Vaccination) – 2 to 4 Days After Visit 1 for Substudy A

- Record AEs as described in Section 8.4.1.
- Record nonstudy vaccinations as described in Section 10.11.6.7.
- Record prohibited medication use as described in Section 10.11.6.7.1.
- Verify understanding of and compliance with protocol requirements for contraception as described in Section 5.3.1.
- Review laboratory results (troponin I) and ECG results. Any abnormal troponin I level must result in further assessments as outlined in Section 10.11.8.8.10.
- Perform 12-lead triplicate ECG. Any new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 10.11.8.4.1) must result in further assessments as outlined in Section 10.11.8.8.10.
- Measure vital signs, including oral temperature, pulse rate, and seated blood pressure.
- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 8.3.4.
- Remind the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Remind the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Remind the participant to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.11.8.8.10).

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

10.11.8.8.4. Visit 3 – 1-Week Follow-Up Visit (After Vaccination) – 6 to 8 Days After Visit 1 for Substudy A

- Record AEs as described in Section 8.4.1.
- Record nonstudy vaccinations as described in Section 10.11.6.7.
- Record prohibited medication use as described in Section 10.11.6.7.1.
- Verify understanding of and compliance with protocol requirements for contraception as described in Section 5.3.1.
- Review laboratory results (troponin I) and ECG results. Any abnormal troponin I level must result in further assessments as outlined in Section 10.11.8.8.10.
- Perform 12-lead triplicate ECG. Any new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 10.11.8.4.1) must result in further assessments as outlined in Section 10.11.8.8.10.
- Measure vital signs, including oral temperature, pulse rate, and seated blood pressure.
- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 8.3.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Review the participant's reactogenicity e-diary data. If the e-diary collection period is complete:
    - Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
    - Collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device (if the visit is conducted after Day 7).

- Remind the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Remind the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Remind the participant to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.11.8.8.10).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.11.8.8.5. Visit 4 – 4-Week Follow-Up Visit (After Vaccination) – 26 to 30 Days After Visit 1 for Substudy A

- Record AEs as described in Section 8.4.1.
- Record nonstudy vaccinations as described in Section 10.11.6.7.
- Record prohibited medication use as described in Section 10.11.6.7.1.
- Verify understanding of and compliance with protocol requirements for contraception as described in Section 5.3.1.
- Review laboratory results (troponin I) and ECG results. Any abnormal troponin I level must result in further assessments as outlined in Section 10.11.8.8.10.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.

- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- If not already completed, collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.4.1.

10.11.8.8.6. Visit 5 – 8-Week Follow-Up Visit (After Vaccination) – 52 to 60 Days After Visit 1 for Substudy A

- Record nonstudy vaccinations as described in Section 10.11.6.7.
- Record prohibited medication use as described in Section 10.11.6.7.1.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Remind the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Record AEs as described in Section 8.4.1.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.4.1.
- Participants who have not received licensed QIV at Visit 1 may receive this, if deemed as required by the investigator.

10.11.8.8.7. Visit 6 – 6-Month Telephone Contact – 175 to 189 Days After Last Study Vaccination for Substudy A

- Contact the participant by telephone.
- Record SAEs as described in Section 8.4.1.
- Record nonstudy vaccinations as described in Section 10.11.6.7.
- Record prohibited medication use as described in Section 10.11.6.7.1.

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.11.8.8.8. SARS-CoV-2 NAAT Results for Substudy A

- A nasal (midturbinate) swab for SARS-CoV-2 NAAT is obtained at the vaccination visit (Visit 1/Day 1).

Research laboratory–generated positive results from the vaccination visit swabs will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare provider at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing, as per local guidance.

10.11.8.8.9. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction for Substudy A

If a Grade 3 local reaction (Section 8.3.5.2), systemic event (Section 8.3.5.3), or fever (Section 8.3.5.4) 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 8.3.5.2), systemic event (Section 8.3.5.3), or fever (Section 8.3.5.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets Grade 4 criteria.

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

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

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

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

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

- Measure body 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 8.3.5.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.3.5.3.
- Assess other findings associated with the reaction and record this on the AE page of the CRF if appropriate.
- The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

10.11.8.8.10. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis for Substudy A

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after study vaccination must be specifically evaluated by a cardiologist for possible myocarditis or pericarditis. The same applies for any participant in whom a new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 10.11.8.4.1) or abnormal troponin I level is observed at Visit 2 or 3.

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

- ECG and
- Measurement of the troponin level

For any participant in whom a new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 10.11.8.4.1) or abnormal troponin I level is observed at Visit 2 or 3, this should be achieved by repeating the assessments with the central vendor(s).

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.

10.11.9. Statistical Considerations – Substudy A

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

10.11.9.1. Statistical Hypotheses for Substudy A

There are no statistical hypotheses in Substudy A.

10.11.9.1.1. Estimands for Substudy A

The estimands corresponding to the primary and secondary objectives are described in the table in Section 10.11.3.

10.11.9.1.2. Multiplicity Adjustment for Substudy A

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

10.11.9.2. Analysis Sets for Substudy A

For purposes of analysis, the following analysis sets are defined in Substudy A:

Population	Description
Screened	All participants who sign the ICD.
Randomly assigned to study intervention	All participants who are assigned a randomization number in the IWR system regardless of whether or not the study intervention was administered.
Evaluable immunogenicity	All participants who are eligible, receive the study intervention to which they were randomized, have blood drawn for assay testing within the specified time frame after vaccination, have at least 1 valid and determinate assay result at the 4-week postvaccination visit, and have no major protocol violations.
mITT immunogenicity	All randomized participants who receive the study intervention and have at least 1 valid and determinate assay result after vaccination.
Safety	All participants who receive the study intervention.

10.11.9.3. Statistical Analyses for Substudy A

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

10.11.9.3.1. General Considerations for Substudy A

Refer to Section 9 for general considerations of statistical analyses.

10.11.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis for Substudy A

Endpoint	Statistical Analysis Methods
Safety	• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (local reactions, systemic events, AEs, and SAEs) for each study intervention by age stratum (18 through 64 and ≥65 years of age) and overall (≥18 years of age).
	• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting abnormal troponin I laboratory values for each study intervention at 2 days and 1 week after vaccination by age stratum (18 through 64 and ≥65 years of age) and overall (≥18 years of age). • Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants with new ECG abnormalities for each study intervention at 2 weeks and 1 week after vaccination by age stratum (18 through 64 and ≥65 years of age) and overall (≥18 years of age).

10.11.9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis for Substudy A

Endpoint	Statistical Analysis Methods
Secondary/ immunogenicity	• HAI GMTs and the associated 2-sided 95% CIs will be provided for each strain, by study intervention, before vaccination and 4 weeks after receipt of the study intervention by age stratum (18 through 64 and ≥65 years of age).

Endpoint	Statistical Analysis Methods
	• HAI GMFRs from before vaccination to 4 weeks after vaccination and the associated 2-sided 95% CIs will be provided for each strain, by study intervention, for each age stratum (18 through 64 and ≥65 years of age). • The proportion of participants achieving HAI seroconversion at 4 and 8 weeks after vaccination, and the proportion of participants with HAI titers ≥1:40 before vaccination and at 4 weeks after vaccination, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided for each strain, by study intervention, for each age stratum (18 through 64 and ≥65 years of age). • The proportion of participants achieving HAI seroconversion at 4 and 8 weeks after vaccination and the proportion of participants with HAI titers ≥1:40 before vaccination and at 4 weeks after vaccination, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided for all strains by study intervention for each age stratum (18 through 64 and ≥65 years of age). • The strains mentioned above refer to the matched seasonal strains (CCI) recommended by WHO. • GMTs and the associated 2-sided 95% CIs will be provided for each strain-specific neutralizing titer before vaccination and 4 weeks after vaccination by study intervention for each age stratum (18 through 64 and ≥65 years of age). • GMFR from before vaccination to 4 weeks after vaccination and the associated 2-sided 95% CIs will be provided for each strain-specific neutralizing titer by study intervention for each age stratum (18 through 64 and ≥65 years of age). • Percentages of participants with seroresponse and the associated 2-sided Clopper-Pearson 95% CIs will be provided at 4 weeks after vaccination for each strain titer, by study intervention, for each age stratum (18 through 64 and ≥65 years of age). • The strain mentioned above refers to the SARS-CoV-2 Omicron BA.4/BA.5 or SARS-CoV-2 reference strain.

10.11.9.3.4. Exploratory Endpoint(s)/Estimand(s) Analysis for Substudy A

Immune response to emerging VOCs	• GMTs of SARS-CoV-2 neutralizing titers for VOCs not already specified, along with the associated 2-sided 95% CIs, will be provided at specific time points for each vaccine group by age stratum (18 through 64 and ≥65 years of age). • GMFRs from baseline (before the study vaccination) to each subsequent time point, percentage of participants with seroresponse at each time point after vaccination, along with the associated 2-sided 95% CIs, may also be provided for each study intervention by age stratum (18 through 64 and ≥65 years of age).
Exploratory	• HAI GMTs and the associated 2-sided 95% CIs will be provided for each strain, by study intervention, before vaccination and 1 and 8 weeks after receipt of the study intervention, by age stratum (18 through 64 and ≥65 years of age). • HAI GMFRs from before vaccination to 1 and 8 weeks after vaccination and the associated 2-sided 95% CIs will be provided for each strain, by study intervention, for each age stratum (18 through 64 and ≥65 years of age). • The proportion of participants achieving HAI seroconversion at 1 and 8 weeks after vaccination, and the proportion of participants with HAI titers ≥1:40 before vaccination and at 1 and 8 weeks after vaccination, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided for each strain, by study intervention, for each age stratum (18 through 64 and ≥65 years of age). • The proportion of participants achieving HAI seroconversion at 1 and 8 weeks after vaccination and the proportion of participants with HAI titers ≥1:40 before vaccination and at 1 and 8 weeks after vaccination, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided for all strains, by study intervention, for each age stratum (18 through 64 and ≥65 years of age). • The strains mentioned above refer to the matched seasonal strains ([redacted]) recommended by WHO. • GMTs and the associated 2-sided 95% CIs will be provided for each strain-specific neutralizing titer before vaccination and 1 and 8 weeks after vaccination, by study intervention, for each age stratum (18 through 64 and ≥65 years of age).

	• GMFR from before vaccination to 1 and 8 weeks after vaccination and the associated 2-sided 95% CIs will be provided for each strain-specific neutralizing titer, by study intervention, for each age stratum (18 through 64 and ≥65 years of age). • Percentages of participants with seroresponse and the associated 2-sided Clopper-Pearson 95% CIs will be provided at 1 and 8 weeks after vaccination for each strain titer, by study intervention, for each age stratum (18 through 64 and ≥65 years of age). • The strain mentioned above refers to the SARS-CoV-2 Omicron BA.4/BA.5 or SARS-CoV-2 reference strain.

10.11.9.3.5. Other Safety Analyses for Substudy A

All safety analyses will be performed on the safety population.

10.11.9.3.5.1. Electrocardiogram Analyses for Substudy A

Participants with ECG abnormalities will be listed. The number and proportion of participants with any new ECG abnormalities after vaccination will be provided by vaccine group by age stratum (18 through 64 and ≥65 years of age) and overall (≥18 years of age).

10.11.9.3.5.2. Other Analyses for Substudy A

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination (ECG, troponin level, cardiac echocardiogram, and/or cardiac magnetic resonance study) will be summarized and listed by vaccine group by age stratum (18 through 64 and ≥65 years of age) and overall (≥18 years of age).

10.11.9.4. Interim Analyses for Substudy A

No formal interim analysis will be conducted for this study phase. As the sponsor is unblinded with respect to participants' study intervention assignments (except for staff routinely interacting with sites), the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions and/or supporting clinical development.

10.11.9.5. Sample Size Determination for Substudy A

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

Approximately 30 participants will be enrolled for each vaccine group in each age stratum (18 through 64 and ≥65 years of age); therefore, a total of approximately 360 participants may be enrolled into the study across 2 age strata.

For safety outcomes in the study, Table 7 shows the probability of observing at least 1 AE for a given true event rate of a particular AE with 30 participants in each vaccine group.

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

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

10.12. Appendix 12: Substudy B (Phase 1/2)

10.12.1. SoA – Substudy B (Phase 1/2)

Visit Number	Screening	201	202	203	204	205
Visit Description	**Screening**	**Vaccination**	**Day 3 Follow- Up Visit**	**1-Week Follow-Up Visit**	**4-Week Follow-Up Visit**	**6-Month Telephone Contact**
Visit Window (Days)	**0 to 28 Days Before Visit 201**	**Day 1**	**2 to 4 Days After Visit 201**	**6 to 8 Days After Visit 201**	**26 to 30 Days After Visit 201**	**175 to 189 Days After Visit 201**
Visit Type/Location	**Site**	**Site**	**Site or Home Health[a]**	**Site or Home Health[a]**	**Site or Home Health[a]**	**Telehealth[b]**
Obtain informed consent	X					
Assign participant number	X					
Obtain demography and medical history data (including confirmed COVID-19 diagnosis or asymptomatic positive SARS-CoV-2 test result [NAAT or antigen test])	X					
Obtain details of medications currently taken	X					
Perform physical examination	X					
Perform clinical assessment[c]		X				
Measure height and weight	X					
Measure vital signs (including oral temperature)	X	X	X	X		
Perform 12-lead triplicate ECG	X	X	X	X		
Collect blood sample for troponin I laboratory testing	~2.5 mL	~2.5 mL[d]	~2.5 mL	~2.5 mL		
Urine pregnancy test (if appropriate)	X	X				
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	
Collect prior COVID-19 and pneumococcal vaccine information	X					
Collect details of any licensed influenza vaccine received in the prior 12 months	X					
Collect nonstudy vaccine information	X	X	X	X	X	X
Collect prohibited medication use			X	X	X	X
Review troponin I and ECG results		X	X	X	X	
Confirm eligibility	X	X				

Visit Number	Screening	201	202	203	204	205
Visit Description	Screening	Vaccination	Day 3 Follow- Up Visit	1-Week Follow-Up Visit	4-Week Follow-Up Visit	6-Month Telephone Contact
Visit Window (Days)	0 to 28 Days Before Visit 201	Day 1	2 to 4 Days After Visit 201	6 to 8 Days After Visit 201	26 to 30 Days After Visit 201	175 to 189 Days After Visit 201
Visit Type/Location	Site	Site	Site or Home Health[a]	Site or Home Health[a]	Site or Home Health[a]	Telehealth[b]
Obtain randomization number and study intervention allocation		X				
Review temporary delay criteria		X				
Collect blood sample for immunogenicity assessment		~15 or ~50 mL[d,e]			~15 or ~50 mL[e]	
Administer study intervention		X				
Assess acute reactions for at least 30 minutes after study intervention administration		X				
Explain to the participant e-diary completion requirements and assist the participant with downloading the application or issue provisioned device if required		X				
Provide thermometer and measuring device		X				
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►		
Review ongoing reactogenicity e-diary symptoms and obtain stop dates				X	X	
Collect AEs and SAEs as appropriate[f,d]	X	X	X	X	X	X
Collect e-diary or assist the participant with deleting application				X	X	

a. Visit may be completed as a home health visit (see Section 10.12.8.2).
b. Visit will be completed as a telehealth visit (see Section 10.12.8.1).
c. Including, if indicated, a physical examination.
d. Prior to vaccination at Visit 201.
e. Only up to 20 participants in Groups 3, 4, and 5 will have 50 mL drawn (see Section 10.12.4.1).
f. AEs are collected from the completion of informed consent through Visit 204. SAEs are collected from the completion of informed consent through the end of study participation. Additionally, any AEs occurring up to 48 hours after blood draws at Visit 204 must be recorded.

10.12.2. Introduction for Substudy B

10.12.2.1. Substudy B Rationale

This Phase 1/2 substudy will describe the safety, tolerability, and immunogenicity of IRV (qIRV, tIRV, or bIRV) when administered in combination with bivalent BNT162b2 (original/Omi BA.4/BA.5). Bivalent BNT162b2 (original/Omi BA.4/BA.5) will be used during Substudy B, as detailed in Table 2. Substudy B will be single-blind (sponsor-unblinded).

10.12.2.2. Background for Substudy B

See Section 2.2.

10.12.2.3. Benefit/Risk Assessment for Substudy B

See Section 2.3.1 for overall study risks. No unique risks are identified for Substudy B.

Benefits to individual participants enrolled in Substudy B may be:

- Receipt of a dose of an efficacious or potentially efficacious COVID-19 vaccine.
- Receipt of a potentially efficacious influenza vaccine at no cost to the participant, and provision of the immunogenicity results in a subset of participants.
- Contributing to research to help others.
- Please see Section 2.3 for details of the SRSDs relating to the study interventions used in Substudy B.

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

Substudy B (Phase 1/2)

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
To describe the safety and tolerability of study interventions in participants 18 through 64 years of age	In participants 18 through 64 years of age, receiving at least 1 dose of study intervention, the percentage of participants with: • Abnormal troponin I laboratory values 2 days and 1 week after vaccination	• Troponin I laboratory parameters detailed in Section 10.2
	In participants 18 through 64 years of age receiving at least 1 dose of study intervention, the percentage of participants with: • New ECG abnormalities 2 days and 1 week after vaccination	• ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in Section 10.12.8.5.1
	In participants 18 through 64 years of age, receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following vaccination in the right arm only • 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	• Local reactions (pain at the injection site, redness, and swelling) in the right arm only • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Immunogenicity[a]	**Secondary Immunogenicity**	**Secondary Immunogenicity**
To describe the immune responses to SARS-CoV-2 and influenza elicited by each study intervention	In participants 18 through 64 years of age complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at each blood sampling time point after influenza vaccination • GMFR from before vaccination to each blood sampling time point after influenza vaccination • The proportion of participants achieving HAI seroconversion[b] for each strain at each blood sampling time point after influenza vaccination • The percentage of participants with HAI titers ≥1:40 for each strain before vaccination and at each blood sampling time point after influenza vaccination	• HAI titers for the matched seasonal strains recommended by WHO

Substudy B (Phase 1/2)

Objectives	Estimands	Endpoints
	In participants 18 through 64 years of age complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at each blood sampling time point after vaccination for each strain • GMFR from before SARS-CoV-2 vaccination to each blood sampling time point after SARS-CoV-2 vaccination for each strain • Percentages of participants with seroresponse[c] at each blood sampling time point after SARS-CoV-2 vaccination for each strain	• SARS-CoV-2 neutralizing titers by strain
Tertiary/Exploratory	**Tertiary/Exploratory**	**Tertiary/Exploratory**
To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern) in participants 18 through 64 years of age	As detailed in the SAP	• SARS-CoV-2 neutralizing titers for variants (under monitoring, of interest, and/or of concern)
To describe the troponin and ECG abnormalities detected in participants who are evaluated for possible cardiac symptoms	As detailed in the SAP	• Troponin I laboratory parameters detailed in Section 10.2 • ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in Section 10.12.8.5.1

a. There are no primary immunogenicity objectives in this study.
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 at least a 4-fold rise at the time point of interest.
c. 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.

10.12.4. Substudy B Design

10.12.4.1. Overall Design for Substudy B

This is a Phase 1/2 substudy to describe the safety, tolerability, and immunogenicity of IRV (qIRV, tIRV, or bIRV) when administered in combination with bivalent BNT162b2 (original/Omi BA.4/BA.5). Bivalent BNT162b2 (original/Omi BA.4/BA.5) will be used during Substudy B, as detailed in Table 2. Bivalent BNT162b2 (original/Omi BA.4/BA.5) was recommended by ACIP in 2022-2023.[29,30] This substudy will be single-blind (sponsor-unblinded).

During Substudy B, up to approximately 630 participants 18 through 64 years of age will be enrolled.

Randomization will be conducted across 3 enrollment cohorts independently due to licensed QIV availability, with enrollment in these cohorts being conducted either concurrently or at different times as required based on operational considerations as shown in Table 8.

Table 8. Substudy B Enrollment Cohorts

Enrollment Cohort	Total Number of Participants	Number of Participants per Vaccine Group	Vaccine Group Number	Vaccine Group Descriptions
1	60	30	1	Licensed QIV (Flucelvax) administered concurrently in the opposite arm to [CC]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5)
			2	Licensed QIV (Flucelvax) administered concurrently in the opposite arm to bIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)
2	360	Up to 120	3	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 1[a]
			4	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 2[a]
			5	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 3[a]
3	210	30	6	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 4[a]
			7	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 5[a]
			8	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 6[a]
			9	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 7[a]
			10	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 8[a]
			11	tIRV/bivalent BNT162b2 (original/Omi\BA.4/BA.5)
			12	qIRV

a. Combinations as shown in Table 2.
Note: * Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Enrollment of participants 18 through 64 years of age will occur only during Substudy B. During Substudy B (Groups 2, 6, 7, 8, 9, 10, 11, and 12), the enrollment will be controlled such that no more than 10 participants (considered sentinel participants) can be vaccinated on the first day; vaccination of the remaining participants will commence no sooner than 24 hours after this safety pause.

Stopping rules will apply to the groups receiving the novel-exploratory combinations of bivalent BNT162b2 (original/Omi BA.4/BA.5) with qIRV, tIRV, and bIRV, as detailed in Section 10.12.8.7.

Safety data accumulated at least 4 weeks following vaccination of participants 18 through 64 years of age in Substudy B will be reviewed by the sponsor's IRC, and if these data are deemed acceptable, the IRC will evaluate which groups (as detailed in Table 2) are acceptable for further study.

Immunogenicity Blood Draws in Substudy B:

Blood samples of approximately 15 mL will be collected for immunogenicity assessments prior to vaccination and at 4 weeks after vaccination. Up to 20 participants in Groups 3, 4, and 5 for the 18- through 64-year age stratum will be asked to consent to alternatively providing 50-mL, rather than 15-mL, blood samples at the same time points, which will be used for immunogenicity assessments as well as assay development/maintenance.

For Substudy B blood draws (as detailed above), up to the first 20 participants who are enrolled first, and who consent, will have the higher-volume blood draws of 50 mL.

All participants will be asked to complete a reactogenicity e-diary for 7 days following each vaccination.

Following vaccination, AEs will be collected from informed consent signing through 4 weeks following each vaccination, and SAEs will be collected from informed consent signing through 6 months after the first vaccination. In addition, AEs will be collected that occur up to 48 hours after blood draws.

10.12.4.2. Scientific Rationale for Study Design for Substudy B

See Section 2.1.

10.12.4.3. Justification for Dose for Substudy B

See Section 4.3.

10.12.4.4. End of Study Definition for Substudy B

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

A participant is considered to have completed the substudy if he/she has completed all periods of the substudy, including the last visit.

10.12.5. Substudy B Population

10.12.5.1. Substudy B Inclusion Criteria

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

Age and Sex:

1. Male or female participants 18 through 64 years of age (or the minimum age of consent in accordance with local regulations) at Visit 201 (Day 1).

    - Refer to Appendix 5 for reproductive criteria for male (Section 10.5.1) and female (Section 10.5.2) participants.

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

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

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

    Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.8.

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. Participants who have received at least 3 prior US-authorized modRNA COVID-19 vaccines, with the last dose being an updated (bivalent) vaccine given at least 150 days before Visit 201. Any dose of modRNA COVID-19 vaccine received after 01 September 2022 may be considered to be a bivalent vaccine in the US.

    Note: Documented confirmation of prior doses of SARS-CoV-2 vaccine received must be obtained prior to randomization.

10.12.5.2. Substudy B Exclusion Criteria

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

Medical Conditions:

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

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

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

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

5. Women who are pregnant or breastfeeding.

6. History of myocarditis or pericarditis.

Prior/Concomitant Therapy:

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

8. 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 60 days before study intervention administration, or planned receipt throughout the study.

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

Prior/Concurrent Clinical Study Experience:

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

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

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

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

Additional Exclusion Criteria:

12. Participation in strenuous or endurance exercise through Visit 203.

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

14. Any abnormal screening troponin I laboratory value.

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

10.12.5.3. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention for Substudy B

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 201 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

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

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

3. Receipt of any nonstudy vaccine within 14 days before study intervention administration at Visit 201.

4. Anticipated receipt of any nonstudy vaccine within 14 days after study intervention administration at Visit 201.

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

10.12.6. Substudy B Intervention and Concomitant Therapy

10.12.6.1. Study Intervention(s) Administered for Substudy B

Study interventions for Substudy B will include:

Intervention Name	BNT162b2[a] CCI [redacted]	qIRV	qIRV[b]/BNT162b2[a]	tIRV[c]/BNT162b2[a]	bIRV[c]/BNT162b2[a]	QIV
Arm Name (group of participants receiving a specific study intervention or no study intervention)	Licensed QIV + BNT162b2[a]	qIRV	qIRV/ BNT162b2[a]	tIRV/ BNT162b2[a]	bIRV/BNT162b2[a] + licensed QIV	Licensed QIV + BNT162b2[a] or Licensed QIV + bIRV/BNT162b2[a]
Targeted Influenza Strains	N/A	Strains as recommended by WHO for recombinant or cell-based influenza vaccines	Strains as recommended by WHO for recombinant or cell-based influenza vaccines	Strains as recommended by WHO for recombinant or cell-based influenza vaccines	Strains as recommended by WHO for recombinant or cell-based influenza vaccines	For each seasonal strain as recommended by WHO
Type	modRNA vaccine	modRNA vaccine	modRNA vaccine	modRNA vaccine	modRNA vaccine	Vaccine
Dose Formulation	modRNA	modRNA	modRNA	modRNA	modRNA	
Unit Dose Strength(s)	CCI [redacted] µg BNT162b2[a]	CCI [redacted] µg qIRV for participants 18 through 64 years of age (as detailed in the IPM)	CCI [redacted] µg or CCI [redacted] µg or CCI [redacted] µg in dose-level combinations as described in the tables titled Substudy B: All Vaccine Groups	CCI [redacted] µg tIRV/ CCI [redacted] µg BNT162b2[a]	CCI [redacted] µg bIRV CCI [redacted] µg BNT162b2[a]	CCI [redacted] µg bIRV/ CCI [redacted] µg BNT162b2[a] As detailed in the IPM
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental

IMP or NIMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided 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. Each PFS or vial will be labeled per country requirement.

a. Bivalent BNT162b2 (original*/Omi BA.4/BA.5) will be used during Substudy B. *Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.
b. Will have formulations that are CCI per the IPM and CCI
c. Formulations will be CCI .

10.12.6.1.1. Administration for Substudy B

See Section 6.1.1.

During Substudy B, participants will receive study intervention at Visit 201 as randomized in accordance with the SoA (Section 10.12.1). All study intervention should be administered intramuscularly into the deltoid muscle of the **right arm**, other than licensed QIV, which should be administered intramuscularly into the deltoid muscle of the left arm.

10.12.6.1.2. Medical Devices for Substudy B

See Section 6.1.2.

10.12.6.1.3. Preparation, Handling, Storage, and Accountability for Substudy B

See Section 6.2.

10.12.6.1.3.1. Preparation and Dispensing for Substudy B

See Section 6.2.1.

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

10.12.6.1.4. Allocation to Study Intervention for Substudy B

See Section 6.3.

Allocation of study intervention at Visit 201 in Substudy B will be conducted via the IRT.

10.12.6.2. Blinding for Substudy B

10.12.6.2.1. Blinding of Participants for Substudy B

Substudy B participants will be blinded to their assigned study intervention.

10.12.6.2.2. Blinding of Site Personnel for Substudy B

Substudy B is single-blind, such that all site personnel, including the investigator, investigator staff, and study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded.

10.12.6.2.3. Blinding of the Sponsor for Substudy B

To facilitate rapid review of data in real time, and to allow an assessment of safety data by study intervention group, sponsor staff will be unblinded to study intervention allocation for the participants enrolled during Substudy B.

10.12.6.2.4. Breaking the Blind for Substudy B

Not applicable.

10.12.6.3. Study Intervention Compliance for Substudy B

See Section 6.5.

10.12.6.4. Dose Modification for Substudy B

Not applicable.

10.12.6.5. Continued Access to Study Intervention After the End of the Study for Substudy B

See Section 6.7.

10.12.6.6. Treatment of Overdose for Substudy B

See Section 6.8.

10.12.6.7. Prior and Concomitant Therapy for Substudy B

For Substudy B, the following concomitant medications and vaccinations will be recorded in the CRF:

- Prior receipt of any COVID-19 vaccine.
- Prior receipt of any pneumococcal vaccine.
- Licensed influenza vaccine, if received during the 12 months prior to enrollment.
- Any vaccinations received from 28 days prior to enrollment until the last visit (Visit 204).
- Prohibited medications listed in Section 10.12.6.7.1, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

10.12.6.7.1. Prohibited During the Study for Substudy B

- 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 201.
- 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.

- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies, from 60 days before study intervention administration through conclusion of the study.

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

10.12.6.7.2. Permitted During the Study for Substudy B

- Medication other than that described as prohibited in Section 10.12.6.7.1 required for treatment of preexisting conditions or acute illness is permitted.

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

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

See Section 7.

10.12.8. Substudy B Assessments and Procedures for Substudy B

For participants in Substudy B, the minimal blood sampling volume is approximately 40 mL (15 mL at Visits 201 and 204 and approximately 2.5 mL at screening and Visits 201, 202, and 203). Up to 20 participants in Groups 3, 4, and 5 in the 18- through 64-year age stratum will be asked to consent to alternatively providing 50-mL, rather than 15-mL, blood samples at the same time points, which will be used for immunogenicity assessments as well as assay development.

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

10.12.8.1. Telehealth Visits for Substudy B

In Substudy B, the final visit will consist of a telehealth visit to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit (see the SoA):

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Procedures as indicated for Visit 205 (Section 10.12.8.9.6).

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

10.12.8.2. Home Health Visits for Substudy B

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

- Procedures as indicated for Visits 202, 203, and 204 (see Section 10.12.8.9.3, Section 10.12.8.9.4, and Section 10.12.8.9.5, respectively).

10.12.8.3. Immunogenicity Assessments for Substudy B

Samples will be collected at the time points specified in Section 10.12.1 from all participants, and the following assays will be performed:

- HAI titers against seasonal strains (CCI), (CCI), and (CCI recommended by WHO.
- SARS-CoV-2 neutralization assay (reference strain).
- SARS-CoV-2 neutralization assays (Omicron BA.4, Omicron BA.5, and other emerging variants [under monitoring, of interest, and/or of concern], including other Omicron sublineages, may also be evaluated).

10.12.8.3.1. N-Binding Antibody Test for Substudy B

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.

10.12.8.4. Biological Samples for Substudy B

See Section 8.2.1.

10.12.8.5. Safety Assessments for Substudy B

See Section 8.3.

10.12.8.5.1. ECGs for Substudy B

ECGs will be collected at the times specified in Section 10.12.1 for Substudy B.

All scheduled 12-lead ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. The ECGs should be obtained **prior** to blood collection, measurement of blood pressure, and measurement of pulse rate. ECGs will be performed in triplicate.

ECG data will be submitted to a central laboratory for evaluation. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (see Section 10.3) and should be evaluated further, as clinically warranted.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that lead placement be in the same position each time during each assessment visit in order to achieve precise ECG recordings.

ECG abnormalities consistent with probable or possible myocarditis or pericarditis are those judged as such by a cardiologist, including:

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

Echocardiograms may be performed as detailed in Section 10.12.8.10.

ECG values of potential clinical concern are listed in Section 10.9.

10.12.8.6. Clinical Safety Laboratory Assessments for Substudy B

Please see Section 8.3.4. Additionally, see Section 10.2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

10.12.8.7. Stopping Rules for Substudy B Groups 2, 6, 7, 8, 9, 10, 11, and 12

The following stopping rules are in place for participants receiving one of the following combinations, not previously covered in Substudy A: qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5), tIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5), or bIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) concurrently with licensed QIV in Substudy B, based on AE, ECG, and laboratory data review. These data will be reviewed 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 in all vaccine groups across both age strata
    - For all participants already vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the conditions listed in the stopping rule criteria below occur within 4 weeks after study intervention administration. Each vaccine group will be evaluated for contribution to stopping rules independently.

Stopping Rule Criteria:

1. If any vaccinated participant develops:
    - A new ECG abnormality that a cardiologist judges consistent with probable or possible myocarditis or pericarditis, including but not limited to:
        - Sustained atrial or ventricular arrhythmias
        - Second-degree Mobitz Type II or worse AV block, new bundle branch block
        - Diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis
    - An abnormal troponin I value that is confirmed abnormal on repeat testing, assessed as related to study intervention by the investigator.
2. If ≥1 vaccinated participant develops a confirmed clinical diagnosis of myocarditis or pericarditis.
3. If any vaccinated participant dies.
4. If ≥1 vaccinated participant experiences a Grade 4 unsolicited AE, or SAE of any severity, assessed as related by the investigator.

5. If ≥2 participants vaccinated with qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5), tIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5), or bIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) given concurrently with licensed QIV, at the same dose level, 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 local reactions, systemic events, and fever specified in Section 8.3.5, 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.

10.12.8.8. Adverse Events, Serious Adverse Events, and Other Safety Reporting for Substudy B

See Section 8.4.

10.12.8.9. Study Procedures for Substudy B

10.12.8.9.1. Screening (0 to 28 Days Before Visit 201) for Substudy B

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 participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain medical history, including confirmed COVID-19 diagnosis (see Section 8.4.7) or asymptomatic positive SARS-CoV-2 test result (NAAT or antigen test), and any other medical history of clinical significance.
- Obtain the details of any medications currently taken.
- Perform 12-lead triplicate ECG.
- Perform physical examination, including vital signs (weight, height, oral temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 8.3.4.
- Perform urine pregnancy test on WOCBP as described in Section 8.3.6.
- Discuss contraceptive use as described in Section 5.3.1.
- Record nonstudy vaccinations as described in Section 10.12.6.7.
- Review documentation of all prior COVID-19 vaccinations. All vaccines must be authorized for use in the US. Record prior receipt of any COVID-19 vaccine as described in Section 10.12.6.7.
- Record prior receipt of any pneumococcal vaccine as described in Section 10.12.6.7.
- Record details of any licensed influenza vaccine received in the prior 12 months, as described in Section 10.12.6.7.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.4.1.
- The investigator or an authorized designee completes the CRF.

10.12.8.9.2. Visit 201 – Vaccination (Day 1) for Substudy B

- It is anticipated that the procedures below will be conducted in a stepwise manner.
- Discuss contraceptive use as described in Section 5.3.1.
- Record nonstudy vaccinations as described in Section 10.12.6.7.
- Review screening central laboratory results (troponin I) and central ECG reports.
- Perform 12-lead triplicate ECG.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF or on the AE CRF as per Section 10.3.
- Measure vital signs, including oral temperature, pulse rate, and seated blood pressure.
- Perform urine pregnancy test on WOCBP as described in Section 8.3.6.

- Ensure that the participant continues to meet all of the inclusion criteria and none of the exclusion criteria.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system.
- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 8.3.4.
- Collect a blood sample (approximately 15 mL or 50 mL), before administration of study intervention, for immunogenicity assessment.
- Site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle per Section 10.12.6.1.1.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary completion requirement to the participant and assist the participant with downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.

- Record AEs as described in Section 8.4.1.
- 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 immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.12.8.10).
- 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 updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.12.8.9.3. Visit 202 – Day 3 Follow-Up Visit (After Vaccination) – 2 to 4 Days After Visit 201 for Substudy B

- Record AEs as described in Section 8.4.1.
- Record nonstudy vaccinations as described in Section 10.12.6.7.
- Record prohibited medication use as described in Section 10.12.6.7.1.
- Verify understanding of and compliance with protocol requirements for contraception as described in Section 5.3.1.
- Review screening central laboratory results (troponin I) and central ECG reports. Any abnormal troponin I level must result in further assessments as outlined in Section 10.12.8.10.
- Perform 12-lead triplicate ECG. Any new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 10.12.8.5.1) must result in further assessments as outlined in Section 10.12.8.10.
- Measure vital signs, including oral temperature, pulse rate, and seated blood pressure.
- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 8.3.4.

- Remind the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Remind the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Remind the participant to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.12.8.10).
- Remind the participant to complete the e-diary, which should be reviewed daily by the site.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.12.8.9.4. Visit 203 – 1-Week Follow-Up Visit (After Vaccination) – 6 to 8 Days After Visit 201 for Substudy B

- Record AEs as described in Section 8.4.1.
- Record nonstudy vaccinations as described in Section 10.12.6.7.
- Record prohibited medication use as described in Section 10.12.6.7.1.
- Verify understanding of and compliance with protocol requirements for contraception as described in Section 5.3.1.
- Review screening central laboratory results (troponin I) and central ECG reports. Any abnormal troponin I level must result in further assessments as outlined in Section 10.12.8.10.

- Perform 12-lead triplicate ECG. Any new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 10.12.8.5.1) must result in further assessments as outlined in Section 10.12.8.10.
- Measure vital signs, including oral temperature, pulse rate, and seated blood pressure.
- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 8.3.4.
- Review the participant's reactogenicity e-diary data. If the e-diary collection period is complete:
  - Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
  - Collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device (if the visit is conducted after Day 7).
- Remind the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Remind the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Remind the participant to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.12.8.10).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.12.8.9.5. Visit 204 – 4-Week Follow-Up Visit (After Vaccination) – 26 to 30 Days After Visit 201 for Substudy B

- Record AEs as described in Section 8.4.1.
- Record nonstudy vaccinations as described in Section 10.12.6.7.
- Record prohibited medication use as described in Section 10.12.6.7.1.
- Verify understanding of and compliance with protocol requirements for contraception as described in Section 5.3.1.
- Review screening central laboratory results (troponin I) and central ECG reports. Any abnormal troponin I level must result in further assessments as outlined in Section 10.12.8.10.
- Collect a blood sample of approximately 15 mL or 50 mL for immunogenicity testing.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- If not already completed, collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.4.1.

10.12.8.9.6. Visit 205 – 6-Month Telephone Contact – 175 to 189 Days After Last Study Vaccination for Substudy B

- Contact the participant by telephone.
- Record SAEs as described in Section 8.4.1.
- Record nonstudy vaccinations as described in Section 10.12.6.7.
- Record prohibited medication use as described in Section 10.12.6.7.1.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.12.8.9.7. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction for Substudy B

If a Grade 3 local reaction (Section 8.3.5.2), systemic event (Section 8.3.5.3), or fever (Section 8.3.5.4) 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 8.3.5.2), systemic event (Section 8.3.5.3), or fever (Section 8.3.5.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets Grade 4 criteria.

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

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

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

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

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

- Measure body 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 8.3.5.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.3.5.3.

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

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

10.12.8.10. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis for Substudy B

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 6 weeks after study vaccination must be specifically evaluated in clinic by a cardiologist for possible myocarditis or pericarditis. The same applies for any participant in whom a new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 10.12.8.5.1) or abnormal troponin I level is observed at Visit 202 or Visit 203.

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

- ECG and

- Measurement of the troponin level

For any participant in whom a new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 10.12.8.5.1) or abnormal troponin I level is observed at Visit 202 or Visit 203, this should be achieved by repeating the assessments with the central vendor(s).

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 of myocarditis or pericarditis is considered an important medical event and must be reported as an SAE (refer to Sections 8.4.1.1 and 8.4.3). Other diagnoses should be recorded as AEs or SAEs, as appropriate. Refer also to Section 8.4.7.

10.12.8.11. Additional Procedures for Monitoring of Potential Menstrual Cycle Disturbances for Substudy B

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, and irregular periods) following receipt of study intervention until 6 months after the first 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.

10.12.8.11.1. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction for Substudy B

If a Grade 3 local reaction (Section 8.3.5.2), systemic event (Section 8.3.5.3), or fever (Section 8.3.5.4) 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 8.3.5.2), systemic event (Section 8.3.5.3), or fever (Section 8.3.5.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets Grade 4 criteria.

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

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

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

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

- Measure oral temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).

- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.3.5.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.3.5.3.
- Assess for other findings associated with the reaction and record these on the AE page of the CRF if appropriate.
- The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

10.12.8.12. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis for Substudy B

During Substudy B, participants 18 through 64 years of age will be closely monitored for potential asymptomatic and symptomatic myocarditis/pericarditis, including the use of routine ECGs and troponin testing.

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 6 weeks after study vaccination must be specifically evaluated in clinic 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 (eg, myocarditis, pericarditis, or other) should be recorded as an AE or SAE, as appropriate. Refer also to Section 8.4.7.

10.12.8.13. Additional Procedures for Monitoring of Potential Menstrual Cycle Disturbances for Substudy B

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, and irregular periods) following receipt of study intervention until 6 months after the first vaccination should be specifically evaluated by the investigator at the next planned visit. Details of the symptoms, menstrual history, and results of any investigations performed will be recorded in the CRF.

10.12.9. Statistical Considerations – Substudy B

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

10.12.9.1. Statistical Hypotheses for Substudy B

There are no statistical hypotheses for Substudy B.

10.12.9.1.1. Estimands for Substudy B

10.12.9.1.1.1. Primary Estimands/Coprimary Estimands for Substudy B

The estimands to evaluate the safety objective are based on the safety population. These estimands estimate vaccine safety after study intervention. Completely missing e-diary data will not be imputed; missing AE dates and missing AE intensity will be handled according to Pfizer safety rules. Missing e-diary data not recorded in the e-diary will be recorded on the AE CRF. Therefore, the primary analysis will use reactogenicity recorded as AEs in the CRF to impute the missing e-diary data.

10.12.9.1.1.2. Secondary Estimands for Substudy B

The secondary estimands corresponding to each secondary objective are described in the table in Section 10.12.3.

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

Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analyses.

10.12.9.1.2. Multiplicity Adjustment for Substudy B

There is no multiplicity adjustment for the study as the study is descriptive in nature.

10.12.9.2. Analysis Sets for Substudy B

For purposes of analysis, the following analysis sets are defined in Substudy B:

Population	Description
Screened	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All participants who are eligible, receive the study intervention(s) to which they were randomized, have blood drawn for assay testing within the specified time frame after vaccination(s), have at least 1 valid and determinate assay result at the 4-week postvaccination visit, and have no major protocol violations.
mITT immunogenicity	All randomized participants who receive the study intervention and have at least 1 valid and determinate assay result after vaccination.
Safety	All participants who receive the study intervention.

Individuals with onset of influenza or COVID-19 during the study period (starting from the time of vaccination/Day 1) may be removed from the evaluable immunogenicity population for influenza or COVID-19, respectively.

10.12.9.3. Statistical Analyses for Substudy B

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

10.12.9.3.1. General Considerations for Substudy B

Refer to Section 9 for general considerations of statistical analyses.

10.12.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis for Substudy B

Endpoint	Statistical Analysis Methods
Primary safety	• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants 18 through 64 years of age reporting abnormal troponin I laboratory values for each study intervention at 2 days and 1 week after vaccination, for all participants. • Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants 18 through 64 years of age with new ECG abnormalities for each study intervention at 2 weeks and 1 week after vaccination, for all participants. • Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (local reactions and systemic events) for each vaccine group, in participants 18 through 64 years of age. • Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (AEs and SAEs) for each vaccine group, in participants 18 through 64 years of age. • AEs and SAEs will be categorized according to MedDRA terms.

10.12.9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis for Substudy B

Endpoint	Statistical Analysis Methods
Secondary immunogenicity (participants 18 through 64 years of age)	**Influenza:** • HAI GMTs, and the associated 2-sided 95% CIs, will be provided for each strain, by study intervention, before vaccination and at 4 weeks after vaccination (primary) and at other postvaccination time points (secondary), for all participants.

Endpoint	Statistical Analysis Methods
	• HAI GMFRs from before vaccination to 4 weeks after vaccination (primary) and to other postvaccination time points (secondary), and the associated 2-sided 95% CIs, will be provided for each strain, by study intervention, for all participants. • The proportion of participants achieving HAI seroconversion at 4 weeks after vaccination (primary) and at other postvaccination time points (secondary) and the proportion of participants with HAI titers ≥1:40 before vaccination and at 4 weeks and 6 months after vaccination, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided for each strain, by study intervention, for all participants. • The strains mentioned above for qIRV or QIV-related study interventions refer to the matched seasonal strains recommended by WHO. **SARS-CoV-2:** • GMTs, and the associated 2-sided 95% CIs, will be provided by study intervention for each strain-specific neutralizing titer before vaccination and at 4 weeks after vaccination (primary) and at other postvaccination time points (secondary), for all participants. • GMFR from before vaccination to 4 weeks after vaccination (primary) and to other postvaccination time points (secondary), and the associated 2-sided 95% CIs, will be provided by study intervention for each strain-specific neutralizing titer, for all participants. • Percentages of participants with seroresponse, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided by study intervention at 4 weeks after vaccination (primary) and at other postvaccination time points (secondary) for each strain, for all participants.

10.12.9.3.4. Tertiary/Exploratory Endpoint(s) for Substudy B

Planned analyses of exploratory endpoints are indicated below.

Immune response to emerging variants (under monitoring, of interest, and/or of concern)	• GMTs of SARS-CoV-2 variant (under monitoring, of interest, and/or of concern) neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified, along with the associated 2-sided 95% CIs, will be provided at specific time points for each study intervention. • GMFRs from baseline (before the study vaccination) to each subsequent time point, and the percentage of participants with seroresponse at each time point after vaccination, along with the associated 2-sided 95% CIs, may also be provided for each study intervention.
To describe the troponin and ECG abnormalities detected in participants who are evaluated for possible cardiac symptoms	• Additional summaries and/or listings of troponin and ECG abnormalities related to primary safety endpoints for participants 18 through 64 years of age may be provided, as detailed further in the SAP.

10.12.9.3.5. Other Safety Analyses for Substudy B

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination (ECG, troponin level, cardiac echocardiogram, and/or cardiac magnetic resonance study) will be summarized and listed by study intervention.

10.12.9.4. Interim Analyses for Substudy B

There are no formal interim analyses planned for this study.

10.12.9.5. Analysis Timing for Substudy B

Analyses (immunogenicity or safety) may be performed at any time (eg, safety data through approximately 1 week after vaccination) for all participants.

Complete safety and immunogenicity analysis will be performed at the end of this substudy.

10.12.9.6. Sample Size Determination for Substudy B

10.12.9.6.1. Immunogenicity for Substudy B

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

Approximately 30 participants/up to 120 participants will be enrolled for each vaccine group for participants of 18 through 64 years of age. A total of up to approximately 630 participants may be enrolled.

10.12.9.6.2. Safety for Substudy B

For safety outcomes in the study, Table 9 shows the probability of observing at least 1 AE for a given true event rate of a particular AE with various sample sizes.

Table 9. Probability of Observing at Least 1 AE by Assumed True Event Rate

Sample Size	Assumed True Rate of an AE	Probability of Observing at Least 1 AE
30	0.5%	14.0%
	1.0%	26.0%
	2.0%	45.5%
	5.0%	78.5%
	7.0%	88.7%
120	0.5%	45.2%
	1.0%	70.1%
	2.0%	91.1%
	5.0%	99.8%
	7.0%	>99.99%

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 5 (15 August 2023)

Overall Rationale for the Amendment:

Protocol revisions in response to partial clinical hold.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Throughout	Added monovalent BNT162b2 (Omi XBB.1.5)	Addition of new monovalent BNT162b2 XBB.1.5 in the vaccine groups	Substantial
Section 1.1: Synopsis	Rationale was updated	To align with XBB.1.5 addition	Substantial
Section 1.1: Synopsis	Objectives were updated	To consider the monovalent BNT162b2 (Omi XBB.1.5) and the separation of the 2 age groups in Substudy B	Substantial
Section 1.1 Synopsis	The overall design was summarized as a paragraph; the bullet points were removed	To bring clarity in the design	Nonsubstantial
Section 1.1: Synopsis	The table titled "Substudy B: All Vaccine Groups" was updated to "Substudy B: All Initial-Enrollment Vaccine Groups for Participants 18 Through 64 Years of Age"	To align with the design	Substantial
Section 1.1: Synopsis	Added a new table titled "Substudy B: All Expanded-Enrollment Vaccine Groups for Participants ≥65 Years of Age" to replace 3 tables titled "Substudy B: qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations," "Substudy B: tIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5)," and "Substudy B: bIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5)"	To align with the new design and bring clarity in the naming of the various vaccine groups	Substantial
Section 1.1: Synopsis	Vaccine preparation table was removed	To improve readability of the synopsis	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1: Synopsis	Table titled "Initial-Enrollment Stage Cohorts in Participants 18 Through 64 Years of Age" was updated	To bring detail on licensed QIV	Nonsubstantial
Section 1.1: Synopsis	Updated IRC review to 4 weeks after vaccination in Substudy A	Safety and immunogenicity review was conducted at least 4 weeks after vaccination in Substudy A	Substantial
Section 1.1: Synopsis	Section was revised to align with changes to the study design	To align with study design	Substantial
Section 1.1: Synopsis	Clarification on the Substudy B enrollment strategy for both initial and expanded phases	Enrollment of the participants 18 through 64 years of age and safety review prior to enrolling the participants ≥65 years of age	Substantial
Section 1.1: Synopsis	Updated the number of participants	To align with the updated enrollment strategy	Substantial
Section 1.1: Synopsis	Exclusion criteria were added to Substudy B	To bring clarity	Substantial
Section 1.1: Synopsis	Substudy B study arm table was updated	To reflect XBB.1.5, placebo, and comparator	Substantial
Section 1.2: Schema	Schema was updated	To reflect the new enrollment strategy and safety review	Substantial
Section 2.1: Study Rationale	Text was edited	To align with the study design	Substantial
Section 2.2: Background	Text and references were revised	To align with the study design	Substantial
Section 2.2.3: Clinical Overview	Text was edited	To align with the study design	Substantial
Section 2.3: Benefit/Risk Assessment	Text was edited	To align with the study design	Substantial
Section 4.3: Justification for Dose	Text was edited; addition of BNT162b2 (Omi XBB.1.5)	To align with the study design	Substantial
Section 6: Study Intervention(s) and Concomitant Therapy	Text was edited; more details were added	To bring clarity on the vaccine groups	Substantial
Section 6: Study Intervention(s) and Concomitant Therapy	Text was edited; Table 2 was edited and split into 2 tables (now Tables 2 and 3); previous Tables 3 and 4 were removed	To bring clarity on the vaccine groups	Substantial
Section 7.1: Discontinuation of Study Intervention	Details were added for participants in Group 14 or 15 who may discontinue study intervention administration	To align with the addition of 2-dose groups	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 8.3.5: Electronic Diary	Added instruction that missed e-diary entries should be included in the AE CRF	To align with regulatory expectations	Nonsubstantial
Section 8.4.1: Time Period and Frequency for Collecting AE and SAE Information	Text added to details of AE collection requirements for participants receiving 2 doses of study intervention	To ensure adequate safety follow-up for those who receive 2 doses	Substantial
Section 8.4.7: Adverse Events of Special Interest	Myocarditis and pericarditis are now considered AESIs for up to 6 weeks (previously 4 weeks) after vaccination	To align with regulatory requirements for COVID-19 vaccines	Substantial
Section 9.3.1: General Considerations	Text was edited	To align with the objectives	Nonsubstantial
Section 10.1.5.1: Data Monitoring Committee	DMC will review safety data and immunogenicity accumulated for at least 4 weeks following vaccination in Substudy A and the initial-enrollment stage of Substudy B, was previously 1 week	To align with regulatory expectations	Substantial
Section 10.2: Appendix 2: Clinical Laboratory Tests	Text was edited	To align with the study design	Nonsubstantial
Section 10.11.4: Substudy A Design	Text was edited	To bring clarity	Nonsubstantial
Section 10.12.1: SoA – Substudy B (Phase 1/2)	Schedule of activities was edited	A visit was added	Substantial
Section 10.12.2.1: Substudy B Rationale	Text was edited	To align with the study design	Substantial
Section 10.12.2.3: Objectives, Endpoints, and Estimands (Substudy B)	Objectives were updated	To align with the study design	Substantial
Section 10.12.4.1: Overall Design (Substudy B)	Text and Table 9 were edited	To align with the study design	Substantial
Section 10.12.5.2: Substudy B Exclusion Criteria	Exclusion criteria were added; prior/concomitant therapy was edited	To bring clarity	Substantial
Section 10.12.6.1: Study Intervention(s) Administered (Substudy B Intervention and Concomitant Therapy)	Substudy B study intervention table was edited; previous Table 10 was removed	To align with the study design; Tables 10 and 2 were combined into 1 table (Table 2)	Substantial
Section 10.12.6.1.1: Administration	Text was edited and previous Table 11 was replaced by text	To add clarity on administration of the vaccines	Substantial
Section 10.12.6.7.1: Prohibited During the Study	Wording has been changed	To bring clarity on the prohibited medication during the study	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.12.6.7.2: Permitted During the Study	Added nonstudy coronavirus and nonstudy influenza vaccine allowance at the 4-week follow-up visit	Allowing participants to receive coronavirus and/or influenza vaccines 4 weeks after administration of study intervention	Substantial
Section 10.12.8: Substudy B Assessments and Procedures	Text was revised	To align with the study design	Substantial
Section 10.12.8.1: Telehealth Visits	Text was edited	To clarify the visits	Nonsubstantial
Section 10.12.8.7: Stopping Rules	Revised stopping rules text and addition of stopping rules criteria	To allow a better safety surveillance after study intervention administration	Substantial
Section 10.12.8.10: Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis	Text was updated	To bring clarity	Nonsubstantial
Section 1.1.1.1.1: Visit 302 – 4-Week Follow-Up Visit (After Vaccination)	Text was removed	There is no PBMC	Nonsubstantial
Section 1.1.1.1.1: Visit 302 – 4-Week Follow-Up Visit (After Vaccination)	Additional study intervention for selected groups. Reminder added to alert participant to option for administration of nonstudy vaccines	To align with the study design	Substantial
Section 1.1.1.1.1: Visit 303 – 8-Week Follow-Up Visit (After Vaccination)	Text was removed	There is no PBMC	Nonsubstantial
Section 1.1.1.1.1: Visit 303 – 8-Week Follow-Up Visit (After Vaccination)	Addition of Visit 303	To align with the study design	Substantial
Section 1.1.1.1.1: Visit 304 – 6-Month Follow-Up Visit (After Vaccination)	Visit 304 is replacing Visit 303	Addition of a visit to align with the study design	Substantial
Section 10.12.8.10: Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis	Text was edited	To bring clarity	Nonsubstantial
Section 10.12.9.1.1.1 Primary Estimands/Coprimary Estimands	Included information on the analysis of missing e-diary data recorded on the AE CRF.	To clarify analysis plan	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.12.9.3.2: Primary Endpoint(s)/Estimand(s) Analysis	Text was edited	To align with the study design	Substantial
Section 10.12.9.6.1: Immunogenicity (Sample Size Determination)	Text was added	To align with the study design	Substantial

Amendment 4 (16 April 2023)

Overall Rationale for the Amendment:

To reflect changes to the study design of Substudy B following sponsor review of Substudy A data from participants 18 through 64 years of age, and to remove references to Phase 3.

Protocol Amendment Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Throughout	Removed references to Phase 3	Design change	Nonsubstantial
Throughout	Section number changes due to removal of sections no longer relevant to the new Substudy B design	Due to the study design change, previous sections no longer needed	Nonsubstantial
Section 1 Protocol Summary	Revisions were made to match updates throughout the body of the protocol	To accommodate the study design change of Substudy B and removal of Phase 3	Substantial
Section 2.1 Study Rationale	Revised with updated information	To accommodate study design changes	Nonsubstantial
Section 2.2.3.3 Combined Influenza and SARS-Cov-2 Vaccines	Added section for clarity	To provide clarity	Nonsubstantial
Section 2.3 Benefit/Risk Assessment	Updated QIV from Fluzone to Flucelvax	To update per the study design	Substantial
Section 2.3.1 Risk Assessment	Updated QIV study intervention information and removed study procedure risks for the current study design	To accommodate study design changes	Substantial
Section 4.3.2 qIRV	Updated per the new study design	To accommodate study design changes	Nonsubstantial
Section 4.3.3 qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5)	Revised per the updated Substudy B study design	To accommodate study design changes	Nonsubstantial
Section 4.3.4 tIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5)	Added a section for justification for the addition of study interventions	To accommodate study design changes	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 4.3.5 bIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5)	Added a section for justification for the addition of study interventions	To accommodate study design changes	Nonsubstantial
Section 6 Study Intervention(s) and Concomitant Therapy	Updated with new study interventions and tables; updated table headers	To update per the new study design	Substantial
Section 7.2 Participant Discontinuation/Withdrawal From the Study	Updated to reference Substudy B information	Updated for the new study design	Nonsubstantial
Section 8.2.1 Biological Samples	Removed references to DNA testing	PBMCs no longer being performed	Substantial
Section 8.3.1 Physical Examinations	Updated with Substudy B–specific information	Updated for the new study design	Substantial
Section 8.3.2 Vital Signs	Updated with Substudy B–specific information	Updated for the new study design	Substantial
Section 8.3.3 Electrocardiograms	Added new hyperlink	Updated for the new study design	Nonsubstantial
Section 8.3.4 Clinical Safety Laboratory Assessments	Updated with references for Substudy B	Updated for the new study design	Substantial
Section 8.3.5 Electronic Diary	Removed reference to the ARI e-diary	Updated for the new study design	Substantial
Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information Substudy A	Updated for the new Substudy B design, to remove references to procedures no longer relevant, and updated the SAE collection period with new visit numbers	Updated for the new study design	Substantial
Section 8.4.6 Cardiovascular and Death Events	Updated section for clarity and the new study design	Updated for clarity	Substantial
Section titled Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs (Substudy B)	Section removed as it no longer fits with the new study design	Updated for the new study design	Substantial
Section 8.4.7 Adverse Events of Special Interest	Section updated with new AESIs	Updated for the new study design	Substantial
Section 8.6.1 Specified Genetics	Removed reference to LCI cases	No longer relevant to the Substudy B design	Substantial
Section 8.9 Health Economics	Added reference to Substudy B and removed obsolete information due to the new study design	Updated per new study design information	Nonsubstantial
Section 10.1.3.1 Electronic Consent	Section added per new protocol template information	Updated in advance of the new protocol template	Substantial
Section 10.1.5.1 Data Monitoring Committee	Removed the reference to EDMC and updated the IRC information for Substudy B	Updated for the new study design	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.1.7 Data Quality Assurance	Updated language to align with the new protocol template	Updated to align with the upcoming protocol template	Nonsubstantial
Section 10.1.9 Study and Site Start and Closure	Updated language to align with the new protocol template	Updated to align with the upcoming template	Nonsubstantial
Section 10.2 Appendix 2: Clinical Laboratory Tests	Updated reference Substudy B and included new hyperlink	Updated for the new study design	Nonsubstantial
Section 10.11.4.1 Overall Design	Updated to reflect changes in the Substudy B design and add new tables	Updated for the new study design	Substantial
Section 10.11.6.1 Study Intervention(s) Administered	Updated with tables with new links for clarity	To provide clarity	Nonsubstantial
Section 10.11.8.8.1 Screening (0 to 28 Days Before Visit 1)	Updated to remove reference to collection of previous study participant numbers	To provide clarity	Nonsubstantial
Section 10.12.1.1 SoA—Initial-Enrollment (Phase 1/2)	Added a new section and SoA table due to the new Substudy B design	Updated for the new study design	Substantial
Section Section 10.12.1.2 SoA—Expanded-Enrollment (Phase 2)	Added a new section and updated the previous SoA table due to the new Substudy B design	Updated for the new study design	Substantial
Section 10.12.2.1 Substudy B Rationale	Updated to provide the rationale for the current study design	Updated for the new study design	Substantial
Section 10.12.2.3 Benefit/Risk Assessment	Updated to align with the new study design	Updated for the new study design	Substantial
Section 10.12.3 Objectives, Endpoints, and Estimands (Substudy B)	Added new objectives, estimands, and endpoints to reflect the new Substudy B design and remove obsolete information; removed previous definitions of LCI, CCI, ILI, confirmed COVID-19, and confirmed severe COVID-19	Updated for the new study design	Substantial
Section 10.12.4.1 Overall Design	Revised and updated the entire section to update text to the current design, remove the obsolete design, and add new tables for the current design	Updated for the new study design	Substantial
Section 10.12.5.1 Substudy B Inclusion Criteria	Updated inclusion criteria 1 and 5 to reflect the study design change	Updated for the new study design	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.12.5.2 Substudy B Exclusion Criteria	Removed previous exclusion criteria 5 and 8; added new exclusion criteria 10 through 13	Updated for the new study design	Substantial
Section 10.12.5.3 Criteria for Temporarily Delaying Enrollment/Randomization /Administration of Study Intervention	Updated with new visit information due to the new study design	Updated for the new study design	Nonsubstantial
Section 10.12.6.1 Study Intervention(s) Administered	Updated the table with new interventions and added the Substudy B: All Vaccine Groups table	Updated for the new study design	Substantial
Section 10.12.6.1.1 Administration	Updated with a new Substudy B intervention schedule and intervention arms	Updated for the new study design	Substantial
Section 10.12.6.1.3.1 Preparation and Dispensing	Removed obsolete information due to the new study design	Updated for the new study design	Nonsubstantial
Section 10.12.6.1.4 Allocation to Study Intervention	Updated to reflect the addition of the expanded-enrollment stage	Updated for the new study design	Nonsubstantial
Section 10.12.6.2.2 Blinding of Site Personnel	Updated to reflect the new blinding design and remove obsolete design information	Updated for the new study design	Substantial
Section 10.12.6.2.3 Blinding of the Sponsor	Updated to reflect the new blinding design and remove obsolete design information	Updated for the new study design	Substantial
Section 10.12.6.2.4 Breaking the Blind	Removed obsolete study design information	Updated for the new study design	Substantial
Section 10.12.6.7 Prior and Concomitant Therapy	Updated to align with the new study visits	Updated for the new study design	Nonsubstantial
Section 10.12.8 Substudy B Assessments and Procedures	Updated to include Substudy B study visits	Updated for the new study design	Substantial
Section 10.12.8.1 Telehealth Visits	Updated as a result of the new study design	Updated for the new study design	Substantial
Section 10.12.8.2 Home Health Visits	Updated to include Substudy B study visits	Updated for the new study design	Substantial
Section 10.12.8.3 Surveillance for COVID-19 and Influenza	Removed the section as it is no longer relevant to the new study design	Removed as unneeded	Substantial
Section 10.12.8.3.1 Antigenic Characterization of Influenza Viruses	Removed the section as it is no longer relevant to the new study design	Removed as unneeded	Substantial
Section 10.12.8.3 Immunogenicity Assessments	Updated due to new objectives for Substudy B	Updated for the new study design	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.12.8.6 ARI Memory Aid	Removed the section as it is no longer relevant to the new study design	Removed as unneeded	Substantial
Section 10.12.8.5.1 ECGs	Added a new section to align with the new study design and monitoring procedures	Added for the new study design	Substantial
Section 10.12.8.6 Clinical Safety Laboratory Assessments	Added a new section to align with the new study design and monitoring procedures	Added for the new study design	Substantial
Section 10.12.8.7 Stopping Rules for Initial-Enrollment Stage in All New Exploratory Groups: 2, 6, 7, 8, 9, 10, 11, and 12	Added a new section to align with the new study design and monitoring procedures	Added for the new study design	Substantial
Section 10.12.8.9 Study Procedures – Initial-Enrollment Group	Added a new section and subsections to align with the new study design and new procedures	Added for the new study design	Substantial
Section 10.12.8.12 Study Procedures – Expanded-Enrollment Group	Added a new section and subsections to align with the new study design and new procedures	Added for the new study design	Substantial
Section 10.12.8.11 Communication and Use of Technology	Removed the section as it is no longer relevant to the new study design	Removed as unneeded	Substantial
Section 10.12.9.1 Statistical Hypotheses	Updated the section per the new study design	Updated per the new study design	Substantial
Section 10.12.9.2 Analysis Sets	Removed information no longer relevant to the new study design	Updated per the new study design	Substantial
Section 10.12.9.3.2 Primary Endpoint(s)/Estimand(s) Analysis	Updated the section per the new study design	Updated per the new study design	Substantial
Section 10.12.9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis	Updated the section per the new study design	Updated the section per the new study design	Substantial
Section 10.12.9.3.4 Tertiary/Exploratory Endpoint(s)	Updated the section per the new study design	Updated the section per the new study design	Substantial
Section 10.12.9.5 Analysis Timing	Section updated with the new analysis timing information as a result of the new study design	Updated per the new study design	Substantial
Section 10.12.9.6 Sample Size Determination	Updated the section and subsections to reflect the new study design and remove obsolete design information	Updated per the new study design	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.12.9.6.2 Safety	Updated the section per the new study design	Updated the section per the new study design	Substantial

Amendment 3 (15 February 2023)

Overall Rationale for the Amendment:

Inclusion of Substudy B: A Phase 2/3 study to describe the safety, tolerability, and immunogenicity of qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5).

Protocol Amendment Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1 Protocol Summary	Revisions were made to match updates throughout the body of the protocol	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 2.1 Study Rationale	Revised with updated information	Availability of more current information	Substantial
Section 2.2.1 SARS-CoV-2	Revised with updated information	Availability of more current information	Substantial
Section 2.2.3 Clinical Overview	Revised with updated information	Availability of more current information	Substantial
Section 2.3 Benefit/Risk Assessment	Specified SRSD for QIV is Fluzone Quadrivalent	To provide clarification	Nonsubstantial
Section 2.3.1 Risk Assessment	Added a risk assessment for QIV and midturbinate swabs, and updated the BNT162b2 Omicron (BA.4/BA.5 sublineage) risks	To add additional information and clarify potential risks	Substantial
Section 2.3.1 Risk Assessment	Added ARI visits to potential visits for collection of midturbinate swabs	New ARI visits will entail swabs listed as a risk in table	Nonsubstantial
Section 2.3.2 Benefit Assessment	Added link to Substudy B	To accommodate the addition of Substudy B (Phase 2/3)	Nonsubstantial
Section 3 Objectives, Endpoints, and Estimands	Added link to Substudy B	To accommodate the addition of Substudy B (Phase 2/3)	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 4.3 Justification for Dose	Removed information under this header and updated the corresponding subsections	Availability of more current information	Substantial
Section 4.3.1 Bivalent BNT162b2 (Original/Omi BA.4/BA.5)	Revised justification to note the FDA's EUA as the reason for the chosen dose	Availability of more current information	Substantial
Section 4.3.2 qIRV	Revised justification of dose based on Phase 3 data in different age groups (18 through 64 and ≥65 years of age)	Availability of more current information	Substantial
Section 5 Study Population	Added links throughout the section to new corresponding Substudy B sections	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 5.5 Criteria for Temporarily Delaying Enrollment/Randomization/ Administration of Study Intervention	• Added the Substudy A and B links • Moved the section content to the Substudy A appendix	To better align to the master protocol format	Nonsubstantial
Section 6 Study Intervention(s) and Concomitant Therapy	Added links throughout the section to new corresponding Substudy B sections	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 6 Study Intervention(s) and Concomitant Therapy	Clarified interventions across both substudies	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 8.2.1 Biological Samples	Added verbiage regarding participants who provide consent for genetic testing	To add exceptions for those that agree to genetic testing of PBMC samples	Substantial
Section 8.2 Efficacy and/or Immunogenicity Assessments	Added link to the corresponding Substudy B section	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 8.3.1 Physical Examinations	Added language specific to Substudies A and B, respectively	Physical exams are required in Substudy A and may be performed in Substudy B	Substantial
Section 8.3.2 Vital Signs	Added language specific to Substudy B	Details the vital signs that are taken for Substudy B	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 8.3.4 Clinical Safety Laboratory Assessments	Added language noting that the clinical safety laboratory assessments are only conducted in Substudy A	Details that the assessments are needed only for Substudy A	Substantial
Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information	Added language specific to the collection times for Substudy B	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 8.4.6 Cardiovascular and Death Events	Added detail on when deaths are recorded	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 8.4.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs (Substudy B)	Added information detailing ARI visits	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 8.4.7 Adverse Events of Special Interest	Added updated information needed to include Substudy B	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 8.4.7 Adverse Events of Special Interest	Clarified that a confirmed COVID-19 diagnosis is an AESI after Visit 201	To provide clarity	Nonsubstantial
Section 8.6.1 Specified Genetics	Added in information regarding genetic testing that was not necessary prior to the amendment	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 8.9 Health Economics	Added language regarding the possible evaluation of medical resource utilization in Substudy B only	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 9 Statistical Considerations	Added links throughout the section to the new corresponding Substudy B sections	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 9.3.1 General Considerations	Added language that for all efficacy endpoints, the analyses will be performed on both the evaluable efficacy population and the mITT efficacy population	To clarify current language	Substantial
Section 10.1.5.1 Data Monitoring Committee	Added Substudy B to the IRC language as well as noted that Substudy B will also use an EDMC	To accommodate the addition of Substudy B (Phase 2/3)	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.1.6 Dissemination of Clinical Study Data	Added links to ClinicalTrials.gov and Pfizer.com	To provide links to areas of accessing data	Nonsubstantial
Section 10.4 Appendix 4: Genetics	Added section as it is applicable with the addition of Substudy B	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 10.5.1 Male Participant Reproductive Inclusion Criteria	Updated and specified contraception use	To align with current recommendations	Substantial
Section 10.5.2 Female Participant Reproductive Inclusion Criteria	Updated link to revised section number	Section numbers have changed	Nonsubstantial
Section 10.8 Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection	Added a section to clarify the allowance of participants with chronic stable HIV, HCV, or HBV infections	To provide clarity	Substantial
Section 10.11.1 SoA – Substudy A (Phase 1)	Updated the order of blood draws	To provide clarity	Nonsubstantial
Section 10.11.3 Objectives, Endpoints, and Estimands (Substudy A)	Updated the objectives and estimands to include the new age stratum	To accommodate the new age stratum	Substantial
Section 10.11.4.1 Overall Design	Updated the design section to include the ≥65 years of age stratum and include how the IRC may allow the study to progress to Phase 2	To accommodate the new age stratum	Substantial
Section 10.11.5.1 Substudy A Inclusion Criteria	• Updated the inclusion criteria to remove the 18 through 64 years of age range and also clarified the addition of participants with chronic stable HIV, HCV, and HBV infections • Updated inclusion criterion 5 to detail the 2 age strata • Added inclusion criterion 6	To provide clarity and allow enrollment of other modRNA SARS-CoV-2 recipients and to add the influenza vaccine criterion	Substantial
Section 10.11.5.2 Substudy A Exclusion Criteria	Updated exclusion criterion 9	To accommodate the new age stratum	Substantial
Section 10.11.5.3 Criteria for Temporarily Delaying Enrollment/Randomization/ Administration of Study Intervention	Moved the content previously in Section 5.5 here to align with the master protocol format	To align sections to the master protocol format	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.11.6.1 Study Intervention(s) Administered	Added a row for targeted influenza strains	To provide clarity	Nonsubstantial
Section 10.11.8.8.2 Visit 1 – Vaccination (Day 1)	Updated the order of blood draws	To provide clarity	Nonsubstantial
Section 10.11.8.8.2 Visit 1 – Vaccination (Day 1)	Updated the injection site in the deltoid muscle by removing reference to the nondominant arm	To update per the PACL	Nonsubstantial
Section 10.11.8.8.6 Visit 5 – 8-Week Follow-Up Visit (After Vaccination) – 52 to 60 Days After Visit 1	Updated visit to allow for participants who had not received licensed QIV at Visit 1 to receive it at Visit 5, if deemed as required by the investigator	To accommodate the new age stratum	Substantial
Section 10.11.9.3.2 Primary Endpoint(s)/Estimand(s) Analysis	Updated the section to include age stratifications	To accommodate the new age stratum	Substantial
Section 10.11.9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis	Updated the objectives and estimands to include the new age stratum and match the updated language throughout the protocol	To accommodate the new age stratum	Nonsubstantial
Section 10.11.9.3.4 Exploratory Endpoint(s)/Estimand(s) Analysis	Updated the objectives and estimands to include the new age stratum and match the updated language throughout the protocol	To accommodate the new age stratum	Nonsubstantial
Section 10.11.9.3.5.1 Electrocardiogram Analyses	Updated the section to include age stratifications	To accommodate the new age stratum	Nonsubstantial
Section 10.11.9.3.5.2 Other Analyses	Updated the section to include age stratifications	To accommodate the new age stratum	Nonsubstantial
Section 10.11.9.5 Sample Size Determination	Updated the section to include age stratifications	To accommodate the new age stratum	Nonsubstantial
Section 10.12 Appendix 12: Substudy B (Phase 2/3)	Section (and all subsections) created to add Phase 2/3 Substudy B to existing protocol	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 10.12.8.1 Telehealth Visits	Added the ability to perform a telehealth visit, when applicable	To accommodate the addition of Substudy B (Phase 2/3)	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.12.8.2 Home Health Visits	Added the ability to perform a home health visit, when applicable	To accommodate the addition of Substudy B (Phase 2/3)	Substantial
Section 10.12.8.10.4.2 Additional Procedures for Monitoring of Potential Menstrual Cycle Disturbances	Added section per new AESI	To accommodate new AESI	Substantial
Section 10.13 Appendix 13: Protocol Amendment History	Added the appendix on the protocol amendment history	To update per the protocol template	Nonsubstantial
Throughout	Removed (22/23) after qIRV	To allow for updates as this protocol may later include substudies within other influenza seasons	Nonsubstantial
Throughout	Updated age ranges throughout the protocol	To accommodate the new age stratum	Nonsubstantial

Amendment 2 (09 December 2022)

Overall Rationale for the Amendment:

Participants ≥65 years of age were added to Substudy A.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 Synopsis, Substudy A	Revisions were made to match updates throughout the body of the protocol	To accommodate the new age stratum	Substantial
Section 2.3.1 Risk Assessment	Added a risk assessment for QIV, midturbinate swabs, and updated BNT162b2 Omicron (BA.4/BA.5 sublineage) risks	To add additional information and clarify potential risks	Substantial
Section 2.2.3 Clinical Overview	Updated the section with new information	To add additional information	Substantial
Section 10.5.1 Male Participant Reproductive Inclusion Criteria	Updated and specified contraception use	To align with current recommendations	Substantial
Section 10.8 Appendix 7: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection	Added a section to clarify the allowance of participants with chronic stable HIV, HCV, or HBV infections	To provide clarity	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.11.3 Objectives, Endpoints, and Estimands (Substudy A)	Updated the objectives and estimands to include the new age stratum	To accommodate the new age stratum	Substantial
Section 10.11.4.1 Overall Design	Updated the design section to include the ≥65 years of age stratum and include how the IRC may allow the study to progress to Phase 2	To accommodate the new age stratum	Substantial
Section 10.11.5.1 Substudy A Inclusion Criteria	• Updated the inclusion criteria to remove the 18 through 64 years of age range and also clarified the addition of participants with chronic stable HIV, HCV, and HBV infections • Updated inclusion criterion 5 to detail the two age strata • Added inclusion criterion 6	To provide clarity and allow enrollment of other modRNA SARS-CoV-2 recipients and add influenza vaccine criterion	Substantial
Section 10.11.5.2 Substudy A Exclusion Criteria	• Updated exclusion criterion 9	To accommodate the new age stratum	Substantial
Section 10.11.8.8.6 Visit 5 – 8-Week Follow-Up Visit (After Vaccination) – 52 to 60 Days After Visit 1	Updated visit to allow for participants who had not received licensed QIV at Visit 1 to receive it at Visit 5, if deemed as required by the investigator	To accommodate the new age stratum	Substantial
Section 10.11.9.3.2 Primary Endpoint(s)/ Estimand(s) Analysis	Updated the section to include age stratifications	To accommodate the new age stratum	Substantial
Section 2.3 Benefit/Risk Assessment	Specified SRSD for QIV is Fluzone Quadrivalent	To provide clarification	Nonsubstantial
Throughout	Removed (22/23) after qIRV	To allow for updates as this protocol may later include substudies within other influenza seasons	Nonsubstantial
Throughout	Updated age ranges throughout the protocol	To accommodate the new age stratum	Nonsubstantial
Section 5.5 Criteria for Temporarily Delaying Enrollment/ Randomization/ Administration of Study Intervention	• Added Substudy A link • Moved the section content to the Substudy A appendix	To better align to the master protocol format	Nonsubstantial
Section 7.2 Participant Discontinuation/Withdrawal From the Study	Added new language for when participants would be discontinued in Substudy A	To provide clarity	Nonsubstantial
Section 8.4.8 Adverse Events of Special Interest	Clarified that a confirmed COVID-19 diagnosis is an AESI after Visit 1	To provide clarity	Nonsubstantial
Section 10.11.1	Updated order of blood draws	To provide clarity	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.11.8.8.2 Visit 1 – Vaccination (Day 1)	Updated order of blood draws	To provide clarity	Nonsubstantial
Section 10.11.5.3 Criteria for Temporarily Delaying Enrollment/ Randomization/Administration of Study Intervention	Moved the content previously in Section 5.5 here to align with the master protocol format	To align sections to the master protocol format	Nonsubstantial
Section 10.11.6.1 Study Intervention(s) Administered	Added a row for targeted influenza strains	To provide clarity	Nonsubstantial
Section 10.11.9.3.3 Secondary Endpoint(s)/ Estimand(s) Analysis	Updated the objectives and estimands to include the new age stratum and match the updated language throughout the protocol	To accommodate the new age stratum	Nonsubstantial
Section 10.11.9.3.4 Exploratory Endpoint(s)/ Estimand(s) Analysis	Updated the objectives and estimands to include the new age stratum and match the updated language throughout the protocol	To accommodate the new age stratum	Nonsubstantial
Section 10.11.9.3.5.1 Electrocardiogram Analyses	Updated the section to include age stratifications	To accommodate the new age stratum	Nonsubstantial
Section 10.11.9.3.5.2 Other Analyses	Updated the section to include age stratifications	To accommodate the new age stratum	Nonsubstantial
Section 10.11.9.5 Sample Size Determination	Updated the section to include age stratifications	To accommodate the new age stratum	Nonsubstantial
Section 10.11.8.8.2 Visit 1 – Vaccination (Day 1)	Updated the injection site in the deltoid muscle by removing reference to the nondominant arm	To update per the PACL	Nonsubstantial
Section 10.12 Appendix 11: Protocol Amendment History	Added the appendix on the protocol amendment history	To update per the protocol template	Nonsubstantial

Amendment 1 (18 October 2022)

Overall Rationale for the Amendment:

The stopping rules for the bivalent BNT162b2 (original/Omi BA.4/BA.5)/qIRV arms have been updated to include the [redacted] µg dose levels. This change was in response to a CBER request.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 Synopsis, Substudy A (Phase 1)	Updated language regarding stopping rules to be inclusive of [redacted] µg dose levels	To align with current recommendations	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.10.8.6 Stopping Rules	Added language to include the [redacted] µg combination arms. Updated stopping rules for clarity because of the additional arms being included	To align with current recommendations	Substantial

10.14. Appendix 14: Abbreviations

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

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices (United States)
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
ARI	acute respiratory illness
AST	aspartate aminotransferase
AV	atrioventricular
AxMP	auxiliary medicinal product
BCR	B-cell receptor
bIRV	bivalent influenza modRNA vaccine
BLQ	below the limit of quantitation
BNT162b2	Pfizer/BioNTech COVID-19 vaccine
CBER	Center for Biologics Evaluation and Research (United States)
CCI	culture-confirmed influenza
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
ChAdOx1-S	ChAdOx1-S (recombinant) SARS-CoV-2 vaccine (AstraZeneca)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
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
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
DBP	diastolic blood pressure
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee

Abbreviation	Term
ECC	emergency contact card
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eICD	electronic informed consent document
eSAE	electronic safety 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)
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition assay
Hbe	hepatitis B e
HbeAg	hepatitis B e antigen
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ID	identification
IgG	immunoglobulin G

Abbreviation	Term
ILI	influenza-like illness
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IRV	influenza modRNA vaccine (bIRV, mIRV, or tIRV)
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block
LCI	laboratory-confirmed influenza
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MCAR	missing completely at random
MDR	medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
mIRV	monovalent influenza modRNA vaccine
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
mRNA	messenger ribonucleic acid
mRNA-1273	mRNA-1273 SARS-CoV-2 vaccine (Moderna)
NA	neuraminidase
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
NI	noninferiority
NIMP	noninvestigational medicinal product
NYHA	New York Heart Association
Omi	Omicron
PACL	protocol administrative change letter
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PFS	prefilled syringe(s)

Abbreviation	Term
PI	principal investigator
PPE	personal protective equipment
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QTcF	QT interval corrected using Fridericia's formula
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SADE	serious adverse device effect
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
Scr	serum creatinine
Scys	serum cystatin C
SD	standard-dose
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
ST-T	ST segment and T wave
SUSAR	suspected unexpected serious adverse reaction
T bili	total bilirubin
TCR	T-cell receptor
Th1	T-helper type 1
tIRV	trivalent influenza modRNA vaccine
TOC	table of contents
UADE	unanticipated adverse device effect
UK	United Kingdom
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States package insert

Abbreviation	Term
VE	vaccine efficacy
VOC	variant of concern
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WT	wild type

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