A PHASE 3, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A COMBINED MODIFIED RNA VACCINE CANDIDATE AGAINST COVID-19 AND INFLUENZA IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech SE
Study Conducted by:	Pfizer Inc.
Study Intervention Number:	PF-07926307
Study Intervention Name:	Combination COVID-19 and Influenza mRNA Vaccine
US IND Number:	28917
EudraCT/EU CT Number:	Not Applicable
ClinicalTrials.gov ID:	NCT06178991
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C5261002
Phase:	3
Sponsor's Agent's Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Combined Modified RNA Vaccine Candidate Against COVID-19 and Influenza

Document History

Document	Version Date
Amendment 2	11 April 2024
Amendment 1	12 January 2024
Original protocol	17 October 2023

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

Protocol Amendment Summary of Changes Table

Amendment 2 (11 April 2024)

Overall Rationale for the Amendment: CCI to include further evaluation of a combined modified flu and Covid-19 vaccine versus standalone vaccines to determine whether combining the vaccines interferes with immune responses.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Added Cohort 3 to enable further evaluation of combined modified flu and Covid-19 vaccine versus standalone vaccines to determine whether the combining the vaccines interferes with immunes responses.	CCI to include Cohort 3 for further evaluation of combined modified flu and Covid-19 vaccine versus standalone vaccine components to determine whether combining the vaccines interferes with immunes responses.	1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 2.1 Study Rationale 2.2.3.2 Influenza 2.2.3.3 Combined Influenza and COVID-19 Vaccines 2.3 Benefit/Risk Assessment 2.3.1 Risk Assessment 2.3.3 Overall Benefit/Risk Conclusion 3 Objectives, Endpoints, and Estimands 4.1 Design

Description of Change	Brief Rationale	Section # and Name
		4.3.2 CCI BNT162b2 (Omi XBB.1.5) and CCI BNT162b2 (Omi XBB.1.5) CCI 5 Study Population 6.1 Study Intervention(s) Administered 6.1.1 Administration 6.3 Assignment to Study Intervention 6.9 Prior and Concomitant Therapy 6.9.1 Prohibited During the Study 6.9.2 Permitted During the Study 8.2 Immunogenicity Assessments 8.10 Study Procedures 9.1 Statistical Hypotheses 9.1.1 Estimands 9.1.2 Multiplicity Adjustment 9.3.3 Secondary Endpoints/Estimands Analysis 9.5.1 Immunogenicity 9.5.2 Safety 11 References
Updated the protocol concerning Cohort 1 enrollment and removed the	CCI	1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 2.1 Study Rationale

Description of Change	Brief Rationale	Section # and Name
corresponding hypotheses.		2.2.3.3 Combined Influenza and COVID-19 Vaccines 3 Objectives, Endpoints, and Estimands 4.1 Design 6.1 Study Intervention(s) Administered 6.3 Assignment to Study Intervention 9.1 Statistical Hypotheses 9.1.2 Multiplicity Adjustment 9.3.2 Primary Endpoints/Estimands Analysis 9.5.1 Immunogenicity
Nonsubstantial Modification(s)		
Adjusted the wording to allow for greater flexibility in evaluating participants, encompassing symptoms beyond the 3 previously specified symptoms.	The updated wording will allow greater flexibility in evaluating participants in timely manner.	8.10.6 Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis
As reflected in PACL 3.0 (29 Jan 2024), the protocol has been updated to include myocarditis and pericarditis wording.	The text has been updated to align with the text used in the standalone BNT162b2 XBB.1.5 wording (which was updated).	8.10.6 Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Description of Change	Brief Rationale	Section # and Name
As reflected in PACL 3.0 (29 Jan 2024), the protocol has been updated to reflect changes to the contact procedure for urgent medical questions directed to the sponsor.	The process for contacting a medically qualified individual has changed from a medical escalation process via a Pfizer Call Center to direct clinical team contact using a Study Team Contact List.	10.1.12 Sponsor's Medically Qualified Individual
As reflected in PACL 3.0 (29 Jan 2024), the protocol has been updated to reflect the retirement of the Emergency Contact Card.	The Emergency Contact Card is being replaced by a study information card and will no longer be referenced.	10.1.12 Sponsor's Medically Qualified Individual
Added minor clarification related to left deltoid reactogenicity and confirm compliance with thermometer instructions.	To further clarify that left deltoid reactogenicity should be considered an AE.	8.3.4.2 Local Reactions 8.3.4.4 Fever 8.4.1 Time Period and Frequency for Collecting AE and SAE Information 8.10.5 Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction
Updated the primary estimands for Cohort 2.	Updated the primary estimands for Cohort 2 for clarity.	1.1 Synopsis 3 Objectives, Endpoints, and Estimands 9.3.2 Primary Endpoints/Estimands Analysis
Added a secondary immunogenicity objective for Cohort 2.	The addition of this secondary immunogenicity objective will allow demonstration of the superiority of HAI immune responses.	1.1 Synopsis 3 Objectives, Endpoints, and Estimands 9.1 Statistical Hypotheses

Description of Change	Brief Rationale	Section # and Name
		9.1.1 Estimands 9.1.2 Multiplicity Adjustment 9.3.3 Secondary Endpoints/Estimands Analysis
Added clarification for the evaluable immunogenicity analysis sets.	To further clarify the evaluable and mITT immunogenicity populations.	9.2 Analysis Sets
Updated the GMR calculation to include unadjusted GMR and model-based GMR.	Made updates in relation to GMR statistics due to the addition of Cohort 3 and changes to the Objectives, Endpoints, and Estimands.	9.3.1.4 Geometric Mean Ratio
Restructured the statistical analysis methods.	To improve clarity of the exploratory endpoints analysis.	9.3.4 Exploratory Endpoints Analysis
Clarified that there is no interim analysis and clarified the timing of planned analysis.	Further clarity regarding the timing of analysis to allow for hypothesis assessment for regulatory purposes.	9.4 Interim Analyses 9.4.1 Analysis Timing
Removed the immunogenicity analysis of Cohort 1 and specified the analysis of Cohort 2 and Cohort 3. Made changes to reflect the updated sample sizes and power analysis for the noninferiority assessments in	Adjustment of immunogenicity sample sizes for Cohort 2 and Cohort 3 and removal of Cohort 1 from the immunogenicity population.	9.5.1 Immunogenicity

Description of Change	Brief Rationale	Section # and Name
Cohort 2 and Cohort 3.		
CCI [redacted]		
Note added to clarify the procedure required if a participant has a change in health status requiring	Ensure it is clear to sites the procedure if a participant has a change in health status requiring them to receive a prohibited vaccine	6.9.1 Prohibited During the Study

Description of Change	Brief Rationale	Section # and Name
them to receive a prohibited vaccine		
Removal of N-binding antibody test to establish exposure to SARS CoV 2	N-binding antibody test will no longer to run to establish exposure to SARS-CoV-2	8.2.1 Testing for SARS-CoV-2 and Influenza Exposure
Changes made to the blinding of the sponsor method	Changes have been made to make it more concise	6.4.3 Blinding of the Sponsor
Addition of dose levels into the study intervention administration table	Addition of this information will allow better understanding of the differences in doses of the vaccines used in this study	1.1 Synopsis 6.1 Study Intervention(s) Administered
Additional clarification entered to ensure sites are reporting AEs and SAEs appropriately	Clarification added to ensure sites report AEs and SAEs appropriately	1.3 Schedule of Activities 2.3.1 Risk Assessment 3 Objectives, Endpoints, and Estimands 4.1 Design 8.4.1 Time Period and Frequency for Collecting AE and SAE Information 8.10.1 Visit 1 – Vaccination (Day 1) 8.10.2 Visit 1A – 1-Week Follow-Up [redacted] – 6 to 8 days After Visit 1 8.10.3 Visit 2 – 4-Week Follow-Up Visit (After Vaccination) – 28 to 35 Days After Visit 1

Description of Change	Brief Rationale	Section # and Name
		8.10.4 Visit 3 – 6-Month Follow-Up Visit (After Vaccination) – 168 to 196 Days After Visit 1
Addition of other key risks identified for BNT162b2 under [redacted]BNT162b2 [redacted]/BNT162b2	Other risks identified text added to the table section for the combination vaccine to cover the BNT162b2 component of the vaccine	2.3.1 Risk Assessment
Made minor typographical changes throughout the protocol.	To correct minor typographical errors.	Title page 1.1 Synopsis 1.2 Schema 2.2.1 SARS-CoV-2 2.2.3.1 SARS-CoV-2 2.3.1 Risk Assessment 2.3.2 Benefit Assessment 2.3.3 Overall Benefit/Risk Conclusion 6.4.3 Blinding of the Sponsor 6.9.1 Prohibited During the Study 7.2 Participant Discontinuation/ Withdrawal From the Study 8.10.1 Visit 1 – Vaccination (Day 1) 8.10.5 Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 9.3.1.1 Analysis for Binary Data

Description of Change	Brief Rationale	Section # and Name
Moved protocol amendment 1 history to the Appendix and renumbered the Appendix sections.	To include changes between the original protocol and protocol amendment 1.	10.12 Appendix 12: Protocol Amendment History 10.13 Appendix 13: Abbreviations

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Observer-Blinded Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Combined Modified RNA Vaccine Candidate Against COVID-19 and Influenza in Healthy Individuals

Brief Title: A Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Combined Modified RNA Vaccine Candidate Against COVID-19 and Influenza

Regulatory Agency Identification Number(s):

US IND Number:	28917
EudraCT/EU CT Number:	Not Applicable
ClinicalTrials.gov ID:	NCT06178991
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C5261002
Phase:	3

Rationale:

The annual vaccine programs in the United States (US), and likely other parts of the world, against both influenza and coronavirus disease 2019 (COVID-19) may be conducted in the future at a similar time of year; therefore, developing a combined vaccine targeting both viruses is likely to generate overall higher vaccination rates for both viruses than if these vaccines were to be administered separately.

The World Health Organization (WHO) recommendation of the composition of influenza virus vaccines in the 2023-2024 northern hemisphere influenza season includes both a quadrivalent and a trivalent vaccine differing by the presence/absence of the B/Yamagata lineage, which has not been seen in circulation since March 2020. At the 05 October 2023 Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting, the committee voted to exclude the B/Yamagata lineage antigen component from quadrivalent influenza vaccines as soon as possible. The initial study design therefore included the flexibility to independently evaluate both trivalent and quadrivalent influenza vaccines when combined with BNT162b2 (the Pfizer-BioNTech COVID-19 vaccine encoding the severe acute respiratory syndrome [SARS-CoV-2] spike protein).

With protocol amendment 2, the study design has been updated based on 2 key developments. First, the ongoing surveillance of influenza strains causing disease burden has further solidified guidance from both the WHO and VRBPAC that influenza vaccines should become trivalent formulations rather than quadrivalent formulations, effective with the 2024/5 northern hemisphere influenza season. CCI [redacted]

CCI [redacted]. Second, the study design has been adapted to include the evaluation of the immunogenicity responses of CCI [redacted]/BNT162b2 as compared to the immunogenicity responses elicited by standalone BNT162b2, QIV (quadrivalent influenza vaccine), and CCI Cohort 3 will be enrolled and randomized to compare the combination vaccine versus these standalone vaccines to determine whether the combination vaccine shows any meaningful interference in immune responses.

C5261001 was a study evaluating modRNA encoding influenza hemagglutinin (HA), either as qIRV or tIRV, in combination with BNT162b2 with a total modRNA vaccine dose level of 90 µg and 75 µg, respectively.

The data demonstrated that these combination vaccine candidates have primarily mild or moderate reactogenicity, consistent with the safety profiles from clinical trials with BNT162b2 and qIRV alone, and no additional safety concerns have been identified. These vaccines elicited immune responses to all vaccine-encoded antigens for both influenza and SARS-CoV-2. The data gathered to date demonstrate that up to a total modRNA dose of 90 µg for the combination vaccine candidates is well tolerated and elicited immune responses against influenza and SARS-CoV-2 vaccine antigens in participants 18 years of age and older. These data support progression to Phase 3 clinical development of selected combination vaccine candidates, CCI /BNT162b2 and/or CCI BNT162b2, up to CCI µg total modRNA for adults 18 through 64 years of age.

The Phase 3 study will evaluate the safety, tolerability, and immunogenicity of selected modRNA vaccine candidates against influenza when combined with BNT162b2 (Omicron [Omi] XBB.1.5), compared to a licensed inactivated QIV administered in the deltoid opposite to that used for administration of BNT162b2 (Omi XBB.1.5), in healthy adults 18 through 64 years of age in Cohort 1 and Cohort 2. Additionally, the study will evaluate the CCI /BNT162b2 combination vaccine candidate in comparison to standalone administration of CCI , BNT162b2 (Omi XBB.1.5) and QIV, to determine whether the combination vaccine shows any meaningful interference in immune responses in Cohort 3. The selected modRNA vaccine dose level and strain to be used in this study are based on Phase 1/2 safety and immunogenicity data, and the dose level and strain information for each vaccine candidate can be found in the study intervention table. For the combination vaccine candidates, a total modRNA dose of CCI µg in a combination of CCI and BNT162b2 and a total modRNA dose of CCI µg in a combination of CCI and BNT162b2 will be used in this study. ModRNA investigational vaccines at doses of CCI and 30 µg BNT162b2 (Omi XBB.1.5), as well as QIV, will be used as comparator vaccines in the enrollment of Cohort 3.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Safety		
To describe the safety and tolerability of study interventions in healthy participants 18 through 64 years of age	• Local reactions (pain at the injection site, redness, and swelling) in the right deltoid only • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • Adverse events (AEs) • Serious adverse events (SAEs)	The percentage of participants 18 through 64 years of age receiving at least 1 dose of study intervention reporting: • Local reactions for up to 7 days following vaccination in the right deltoid 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
Immunogenicity		
To demonstrate that the HAI immune response elicited by CCI BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) (Cohort 2)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains (CCI) recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) • The difference in percentage of participants achieving seroconversion[a] at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5).
To demonstrate that the SARS-CoV-2 immune response elicited by CCI BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV (Cohort 2)	• SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers	In evaluable immunogenicity participants: • GMR of SARS-CoV-2–neutralizing titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) compared to participants who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV • The difference in percentages of participants with seroresponse[b] to the SARS-CoV-2 Omicron (XBB.1.5) strain at 4 weeks after vaccination compared to participants who received CCI BNT162b2 (Omi XBB.1.5) and to those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
Immunogenicity		
To demonstrate that the HAI immune response elicited by CCI BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by QIV alone (Cohort 3)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains CCI recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received QIV alone
To demonstrate that the SARS-CoV-2 immune response elicited by CCI BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by BNT162b2 (Omi XBB.1.5) alone (Cohort 3)	• SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers	In evaluable immunogenicity participants: • GMR of SARS-CoV-2–neutralizing titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) alone
To demonstrate that the HAI immune response elicited by CCI BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by CCI alone (Cohort 3)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains CCI recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received CCI alone
To demonstrate that the HAI immune response elicited by CCI BNT162b2 (Omi XBB.1.5) is superior to that elicited by QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) (Cohort 2)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains CCI recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) • The difference in percentage of participants with seroconversion[a] to the seasonal strain CCI at 4 weeks after vaccination between participants who received CCI BNT162b2 (Omi XBB.1.5) and those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5)

a. Seroconversion is defined as an HAI titer <1:10 prior to vaccination and ≥1:40 at the postvaccination time point of interest, or an HAI titer of ≥1:10 prior to vaccination with a minimum 4-fold rise at the postvaccination time point of interest.
b. Seroresponse is defined as achieving a postvaccination ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the lower limit of quantitation (LLOQ), the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

Overall Design:

This is a Phase 3 observer-blinded study to evaluate the safety, tolerability, and immunogenicity of combined modified RNA candidates. The vaccine candidates are divided into 3 cohorts, which will be studied in a staggered manner, as required by the clinical plan.

All the dose levels used in this study are detailed in the study intervention table.

Cohort 1: Approximately 450 participants 18 through 64 years of age will be enrolled and randomized in a 2:1 ratio by site-based randomization to 1 of the following:

- **Arm A:** CCI /BNT162b2 (Omi XBB.1.5) administered in the right deltoid and placebo administered in the left deltoid, concurrently.
- **Arm B:** 30 µg BNT162b2 (Omi XBB.1.5) administered in the right deltoid and licensed QIV (CCI) administered in the left deltoid, concurrently.

Enrollment of Cohort 1 will be paused in the IRT after randomization of approximately 450 participants into Cohort 1. Safety data (including electronic diary [e-diary] reactogenicity data, SAEs, AEs, and AESIs) of approximately 450 vaccinated participants will be evaluated by the external data monitoring committee (EDMC) after 60 days, CCI

CCI

Cohort 2: Approximately 4500 participants 18 through 64 years of age will be enrolled and randomized in a 2:1 ratio by site-based randomization to 1 of the following:

- **Arm C:** CCI /BNT162b2 (Omi XBB.1.5) administered in the right deltoid and placebo administered in the left deltoid, concurrently.
- **Arm D:** 30 µg BNT162b2 (Omi XBB.1.5) administered in the right deltoid and licensed QIV CCI) administered in the left deltoid, concurrently.

Cohort 3: Approximately 3600 participants will be enrolled and randomized in a 2:2:1:1 ratio by site-based randomization to 1 of the following:

- **Arm E:** CCI /BNT162b2 (Omi XBB.1.5) administered in the right deltoid.
- **Arm F:** 30 µg BNT162b2 (Omi XBB.1.5) administered in the right deltoid.

- **Arm G:** licensed QIV CCI [redacted] administered in the right deltoid.
- **Arm H:** CCI [redacted] administered in the right deltoid.

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

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

CCI [redacted]

Number of Participants:

Cohort 1: Approximately 450 participants will be enrolled.

Cohort 2: Approximately 4500 participants will be enrolled.

Cohort 3: Approximately 3600 participants will be enrolled.

Study Population:

The inclusion and exclusion criteria are listed below and are the same for **all cohorts**.

Inclusion Criteria:

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

- Participants 18 through 64 years of age (or the minimum age of consent in accordance with local regulations) at Visit 1.
- Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

Exclusion Criteria:

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

- 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.
- Vaccination with any investigational or licensed COVID-19 vaccine within 6 months (175 days) before study intervention administration.

Study Arms and Duration:

The study duration for each participant will be approximately 6 months. The CCI [redacted] dose levels when in combination with BNT162b2 (Omi XBB.1.5) to be used in this study are based on Phase 1/2 safety and immunogenicity data and are detailed in the study intervention table.

Intervention Name	CCI [redacted] BNT162b2 (Omi XBB.1.5)	CCI [redacted] BNT162b2 (Omi XBB.1.5)	QIV (CCI [redacted])	CCI [redacted]	BNT162b2 (Omi XBB.1.5)	Normal saline placebo
Use	Experimental	Experimental	Comparator	Experimental	Comparator	Placebo
Investigational Medicinal Product (IMP) or Noninvestigational Medicinal Product (NIMP)/Auxiliary Medicinal Product (AxMP)	IMP	IMP	IMP	IMP	IMP	IMP
Dose Formulation	modRNA	modRNA	Suspension for injection	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	[redacted] µg	[redacted] µg	60 µg HA per 0.5-mL dose	[redacted] µg	30 µg	N/A

Dosage Level(s)	CCI [redacted] µg BNT162b2 (Omi XBB.1.5)	CCI [redacted] µg BNT162b2 (Omi XBB.1.5)	60 µg	CCI [redacted]	30 µg BNT162b2 (Omi XBB.1.5)	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection

Statistical Methods:

The planned sample size for this study is based on the requirement to generate an adequate safety database for licensure and to demonstrate immunological noninferiority (NI) objectives with sufficient statistical power. NI of immune response for the immunogenicity primary objectives (Cohort 2) will be assessed based on the HAI antibody GMRs, SARS-CoV-2 GMR using a CCI [redacted] margin, and both HAI antibody seroconversion rates and SARS-CoV-2 seroresponse rates using a CCI [redacted]% margin. After the immunogenicity primary NI objective (Cohort 2) is established, superiority of HAI immune response objective (Cohort 2) is established, superiority of HAI immune objective (Cohort 2) will be assessed sequentially. NI of immune response for the immunogenicity secondary objectives (Cohort 3) will be assessed based on the HAI antibody GMRs or SARS-CoV-2 GMR using a CCI [redacted] margin. NI immunogenicity primary objectives in Cohort 2 and immunogenicity secondary objectives in Cohort 3 will be evaluated independently.

The safety primary objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each vaccine group. A 3-tier approach will be used to summarize AEs.

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 and the data from nonclinical and clinical trials with CCI [redacted] standalone and CCI [redacted] when in combination with BNT162b2, support a favorable benefit/risk profile and support clinical development of a vaccine combining these components. Considering the measures to minimize risk to study participants, the potential risks association with the study intervention are justified by the anticipated benefits that may be afforded to healthy participants.

Local reactions in the right arm, 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.

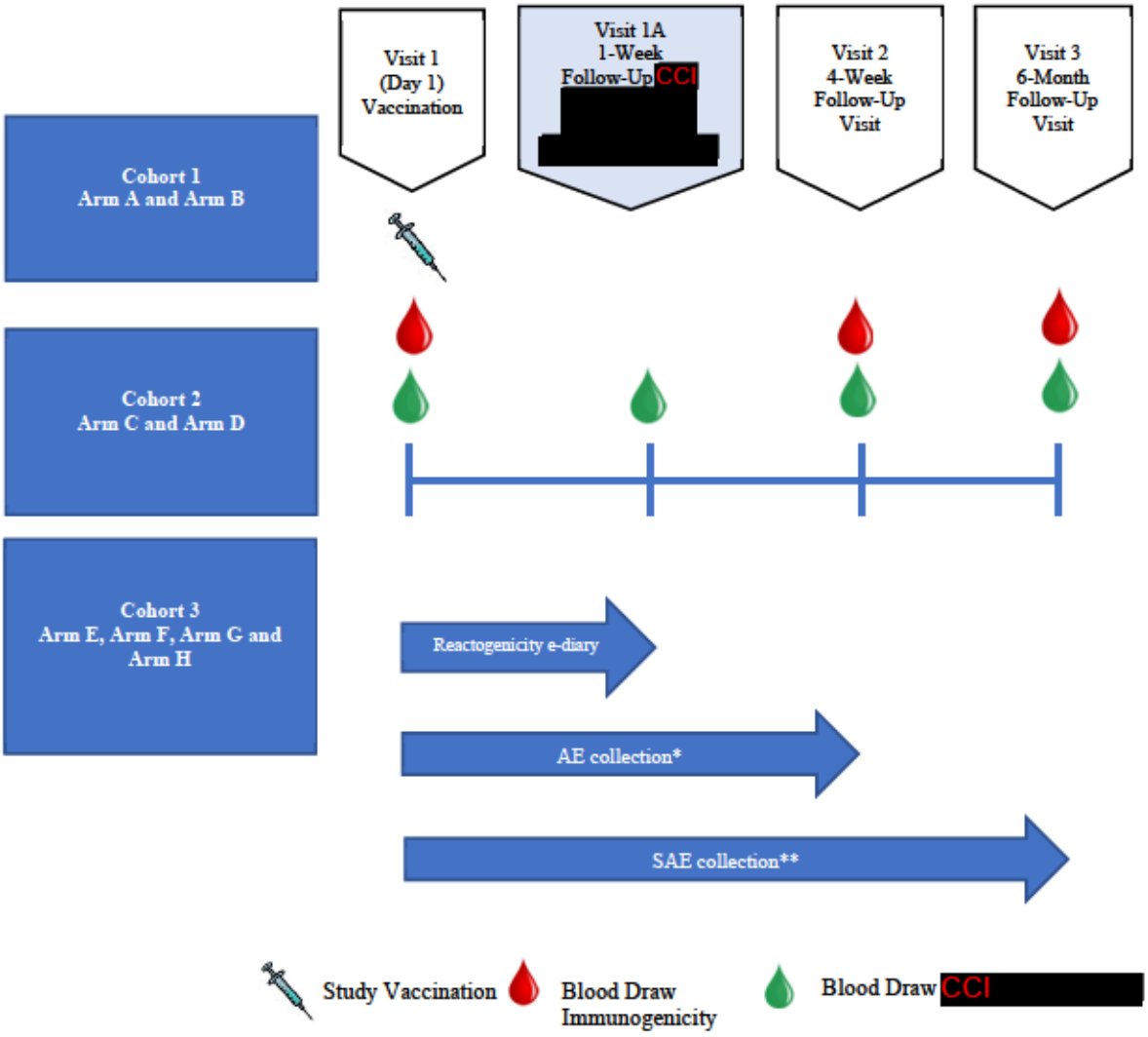
Very rare cases of myocarditis and pericarditis have been reported after authorization in recipients of BNT162b2.

- Cases of anaphylaxis have been reported; however, the frequency is not estimable from the available data.

The study procedure–related risks include:

- Venipuncture will be performed during the study.

1.2. Schema



***Additionally, any AEs occurring up to 48 hours after any subsequent blood draws that are related to study procedures must be recorded in the CRF.**

****Please note the specific time periods for AESI reporting; myocarditis/pericarditis will be collected through 6 weeks. CCI and menstrual disturbances will be collected through 6 months.**

Note: For further details on each cohort, refer to Section 6.1.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures for all cohorts. 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.

Visit Identifier	1	1A	2	3	Notes
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**168 to 196 Days After Visit 1**	
Visit Description	**Vaccination**	**1-Week Follow-Up Visit[a]**	**4-Week Follow-Up Visit**	**6-Month Follow-Up Visit**	Visit 2 and Visit 3 may be performed as telehealth visits if the participant has been discontinued from further study procedures (see Section 7.1 and Section 7.2 for further details).
Obtain informed consent	X				• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
Assign participant number	X				
Obtain demography and medical history data	X				
Obtain details of medications currently taken	X				
Perform clinical assessment, including oral temperature[b]	X				
Measure height and weight	X				See Section 8.3.1 for additional information.
Collect nonstudy vaccine information, including COVID-19 and influenza vaccine information	X	X	X	X	See Section 6.9.1 for additional information.
Collect prohibited medication use	X	X	X	X	See Section 6.9.1 for additional information.

Visit Identifier	1	1A	2	3	Notes
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**168 to 196 Days After Visit 1**	
Visit Description	**Vaccination**	**1-Week Follow-Up Visit[a]**	**4-Week Follow-Up Visit**	**6-Month Follow-Up Visit**	Visit 2 and Visit 3 may be performed as telehealth visits if the participant has been discontinued from further study procedures (see Section 7.1 and Section 7.2 for further details).
Perform urine pregnancy test on WOCBP	X				See Section 8.3.5 for additional information.
Confirm use of contraceptives (if appropriate)	X	X	X		See Section 5.3.1 for additional information.
Confirm eligibility	X				See Section 5 for additional information.
Review temporary delay criteria	X				See Section 5.4 for additional information.
Collect blood sample for immunogenicity assessment	~20 mL		~20 mL	~20 mL	See Section 8.2 for additional information. • See Appendix 2 for a list of clinical laboratory tests to be done. • For laboratory collection volumes, see the laboratory manual.
CCI					
Obtain randomization number and study intervention allocation	X				
Administer study intervention	X				
Postvaccination observation (at least 30 minutes) and assessment of immediate events	X				
Explain participant communication methods (including for reactogenicity e-diary completion), assist the participant with downloading the application, or issue provisioned device, if required	X				See Section 8.3.4 for additional information.

Visit Identifier	1	1A	2	3	Notes
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**168 to 196 Days After Visit 1**	
Visit Description	**Vaccination**	**1-Week Follow-Up Visit[a]**	**4-Week Follow-Up Visit**	**6-Month Follow-Up Visit**	Visit 2 and Visit 3 may be performed as telehealth visits if the participant has been discontinued from further study procedures (see Section 7.1 and Section 7.2 for further details).
Provide/ensure the participant has a thermometer and measuring device	X				
Review reactogenicity e-diary data (daily review is optimal during the active reactogenicity e-diary period [Days 1 through 7])	◄	——— ►			
Site reviews e-diary data with participant follow-up until ongoing symptom/medication resolution, if applicable[d]		X	X		
Collect reactogenicity e-diary medication use		X	X		
Collect AEs, SAEs, and AESIs as appropriate[e]	X	X	X	X	See Section 8.4 and Section 8.4.8 for additional information.
Collect e-diary or assist the participant with deleting the application			X		

a. CCI [redacted] Refer to Section 8.10.2 for further details.
b. Including, if clinically indicated, a physical examination.
c. CCI [redacted]
d. Review the participant's e-diary data and record assessment in the CRF. Assess compliance, any medically attended events (including hospitalizations). For symptoms still ongoing, continue to follow up until resolution, and document and record stop dates in the CRF.
e. AEs are collected from the completion of informed consent through Visit 2. SAEs are collected from the completion of informed consent through the end of study participation. Additionally, any AEs occurring up to 48 hours after a blood draw and deemed related to study procedures must be recorded in the CRF.

2. INTRODUCTION

2.1. Study Rationale

The 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; therefore, developing a combined vaccine targeting both viruses is likely to generate overall higher vaccination rates for both viruses than if these vaccines were to be administered separately.

The WHO recommendation for the composition of influenza virus vaccines in the 2023-2024 northern hemisphere influenza season[1] includes both a quadrivalent and a trivalent vaccine differing by the presence/absence of the B/Yamagata lineage, which has not been seen in circulation since March 2020.[2] At the 05 October 2023 VRBPAC meeting, the committee voted to exclude the B/Yamagata lineage antigen component from quadrivalent influenza vaccines as soon as possible.[3] The initial study design therefore included the flexibility to independently evaluate both trivalent and quadrivalent influenza vaccines when combined with BNT162b2.

With protocol amendment 2, the study design has been updated based on 2 key developments. First, the ongoing surveillance of influenza strains causing disease burden has further solidified guidance from both the WHO and VRBPAC that influenza vaccines should become trivalent formulations rather than quadrivalent formulations, effective with the 2024/5 northern hemisphere influenza season.[4,5] CCI [redacted] Second, the study design has been adapted to include the evaluation of the immunogenicity responses of CCI /BNT162b2 as compared to the immunogenicity responses elicited by standalone BNT162b2, QIV, and CCI Cohort 3 will be enrolled and randomized to compare the combination vaccine versus these standalone vaccines to determine whether the combination vaccine shows any meaningful interference in immune responses.

C5261001 was a study evaluating modRNA encoding influenza HA as a quadrivalent vaccine, qIRV, or a trivalent vaccine, tIRV, in combination with BNT162b2 with total modRNA vaccine dose levels of up to 90 µg. The data demonstrated that these combination vaccine candidates have primarily mild or moderate reactogenicity, consistent with the safety profiles from clinical trials with BNT162b2 and qIRV alone, and no additional safety concerns have been identified. These vaccines elicited immune responses to all vaccine-encoded antigens for both influenza and SARS-CoV-2.

C5261001 Substudy B is a Phase 1/2 substudy with safety and immunogenicity data being collected for qIRV/BNT162b2 combinations of up to 90 µg total modRNA, as well as a tIRV/BNT162b2 combination of 75 µg total modRNA. The data gathered to date demonstrate that up to a total modRNA dose of 90 µg for the combination vaccine candidates is well tolerated and elicited immune responses against influenza and SARS-CoV-2 vaccine antigens in participants 18 years of age and older. These data support progression to Phase 3 clinical development of selected combination vaccine candidates, CCI /BNT162b2 and/or

[redacted] BNT162b2, up to [redacted] µg total modRNA dose for adults 18 through 64 years of age (refer to Section 6.1).

The Phase 3 study will evaluate the safety, tolerability, and immunogenicity of selected modRNA vaccine candidates against influenza when combined with BNT162b2 (Omi XBB.1.5) compared to a licensed inactivated QIV administered in the deltoid opposite to that used for administration of BNT162b2 (Omi XBB.1.5) in healthy adults 18 through 64 years of age in Cohort 1 and Cohort 2. Additionally, the study will evaluate the [redacted]/BNT162b2 combination vaccine candidate in comparison to standalone administration of [redacted] BNT162b2 (Omi XBB.1.5), and QIV in Cohort 3.

The selected modRNA vaccine dose levels and strains for the combination vaccines to be used in this study are based on Phase 1/2 safety and immunogenicity data (refer to Section 10.11). For the combination vaccine candidates, a total modRNA dose of [redacted] µg in a combination of [redacted] and BNT162b2 (Omi XBB.1.5) and a total modRNA dose of [redacted] µg in a combination of [redacted] and BNT162b2 (Omi XBB.1.5) will be used in this study (refer to Section 6.1). ModRNA investigational vaccines at doses of [redacted] and 30 µg BNT162b2 (Omi XBB.1.5), as well as QIV, will be used as comparator vaccines in the enrollment of Cohort 3.

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.[6,7] Therefore, vaccines targeting the spike protein of SARS-CoV-2 have been used as a critical mitigation strategy for 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 newly emerging variants.

BNT162b2 (Comirnaty®) is an mRNA-based vaccine that, as of January 2023, has been approved in 149 countries for the prevention of COVID-19 caused by SARS-CoV-2.[8] 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.[9]

With high background rates of population seropositivity, bivalent (original/Omi BA.4/BA.5) mRNA vaccines continued to provide effective protection against Omicron-related COVID-19,[10,11,12,13,14,15] including during periods of early XBB sublineage dominance.[11] Additional bivalent (original/Omi BA.4/BA.5) mRNA doses have been reported to have higher VE against Omicron than the original vaccine,[16] supporting the hypothesis that better strain-matched vaccines improve protection against COVID-19. However, as of May 2023, the descendent sublineages of Omicron XBB (eg, XBB.1.5, XBB.1.16, XBB.1.9, XBB.2.3) have shown improved transmissibility and reduced susceptibility to neutralization by the

currently available COVID-19 vaccines (bivalent original/Omi BA.4/BA.5) compared to earlier Omicron strains (eg, BA.1, BA.4, BA.5).[10,17] Multiple reports have suggested potential waning VE of bivalent BA.4/BA.5 mRNA vaccination against severe illness, as well as less severe endpoints (ie, urgent/emergency care), roughly 2 to 6 months following vaccination.[15,18,19] These data suggest that continual virus evolution toward improved viral fitness, immune escape, and transmission is impacting VE over time.[20]

2.2.2. Influenza

Influenza is a major cause of morbidity and mortality worldwide, occurring in annual seasonal epidemics and occasionally in global pandemics.[21] Symptomatic influenza infection causes a febrile illness with respiratory and systemic symptoms,[22] although it may often be asymptomatic.[23] 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,[24] while the annual global number of deaths is estimated to range from almost 300,000 to over 600,000.[25]

Influenza viruses are part of the Orthomyxoviridae family and are divided into 4 genera (3 of which are known to infect humans [A, B, and C]) based upon antigenic differences in the nucleoprotein and the matrix protein. Influenza A viruses are further classified into subtypes based upon the membrane glycoproteins, HA and NA.[26] The RNA genome is segmented, which allows genetic reassortment among viruses of the same type.[26] 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.[24] This genetic instability is what necessitates vaccines that are tailored annually.[24]

There is a recommendation in the US for routine annual influenza vaccination for all persons aged ≥6 months who do not have contraindications.[27] Since 2012, the majority of licensed influenza vaccinations in the US have contained 4 influenza strains[28]; however, WHO met in February 2023[1] to review this, as B/Yamagata strains have not been in circulation since March 2020.[2] Based on the 05 Oct 2023 VRBPAC recommendations, the committee voted to exclude the B/Yamagata lineage antigen component from quadrivalent influenza vaccines as soon as possible.[3] The study design therefore includes the flexibility to evaluate both trivalent and quadrivalent influenza vaccines when combined with BNT162b2 independently.

2.2.3. Clinical Overview

2.2.3.1. SARS-CoV-2

Study C4591001 (NCT04368728) was a Phase 1/2/3 trial in ~46,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from an RNA-based vaccine candidate.[29] The trial was conducted in a heterogeneous study population: eligible participants ≥12 years of age who are healthy, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants.

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.[30] 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.[29]

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.[31]

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.[32] 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 previously reported safety 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 vaccine. In the older age group (>55 years of age) 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 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.[33]

Related to this series of developments is the C4591044 study (NCT05472038). C4591044 is an ongoing Phase 2/3, randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of bivalent variant vaccines at the standard or higher dose level. 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. NI 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, NI 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 suggested 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.

Data on SARS-CoV-2 evolution indicated that XBB sublineages accounted for more than 95% of the circulating virus variants in the US as of late June 2023.[17] By several measures, including escape from antibody neutralization and waning protection, the currently available bivalent COVID-19 (original plus Omicron BA.4/BA.5) vaccines appear less effective against currently circulating variants (eg, XBB-lineage viruses, including XBB.1.5) than against previous strains of the virus.[11,12] The totality of available evidence supported that a monovalent XBB-lineage vaccine was warranted for the 2023-2024 update.[9]

The EMA released guidance on 06 June 2023 recommending that a monovalent vaccine targeting the XBB.1 descendent lineages be administered beginning in autumn 2023.[34] On 11 September 2023, the FDA approved authorization of a monovalent vaccine targeting the XBB.1.5 Omicron subvariant.[35,36] On 13 December 2023, the WHO issued a statement on the antigen composition of COVID-19 vaccines, continuing to recommend use of a monovalent formulation with XBB.1.5 as the vaccine antigen.[10]

Study C4591054 is currently evaluating 30 µg of monovalent variant-adapted BNT162b2 (Omi XBB.1.5) in approximately 700 participants ≥12 years of age. It is a Phase 2/3 study investigating the safety, tolerability, and immunogenicity of BNT162b2 (Omicron XBB.1.5) at 30 µg in healthy participants ≥12 years of age, and this dose level will also be used in this study when BNT162b2 (Omi XBB.1.5) is administered alone and as part of the CCI /BNT162b2 (Omi XBB.1.5) combination vaccine or the CCI BNT162b2 (Omi XBB.1.5) combination vaccine.

2.2.3.2. Influenza

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

C4781001 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 modRNA encoding influenza strains in doses up to CCI µg, bivalent modRNA encoding 2 influenza strains in doses up to CCI µg total modRNA dose), quadrivalent modRNA encoding 4 influenza strains in doses up to CCI µg total modRNA dose), and combinations of monovalent and bivalent modRNA vaccines given concomitantly or staggered with licensed influenza vaccines.

The data gathered in this study have demonstrated that a single dose of qIRV (CCI µg or CCI µg total modRNA dose) 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 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 (CCI µg total modRNA dose in adults 18 through 64 years of age and CCI µg total modRNA dose in adults ≥65 years of age).

C4781004 is a Phase 3 study that initiated dosing in adults 18 years of age and older in September 2022. This 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 and ≥65 years of age, respectively. Based on the randomization scheme, this reflects a safety database of over 9000 participants in each age cohort who have received a dose of modRNA influenza vaccine at each dose level. Safety data from this study are continuing to be reviewed by an independent data monitoring committee.

In October 2023, Pfizer disclosed results from its pivotal Phase 3 study evaluating its first-generation modRNA influenza vaccine candidate.[37] Both primary efficacy endpoints were met in the 18- through 64-year-old cohort, demonstrating NI to the licensed comparator. Both primary and end-of-season efficacy analyses considered both influenza A and B cases collectively, though the majority of cases in the 18- through 64-year-old cohort and the 2022/2023 influenza season overall were influenza A cases. Secondary immunogenicity endpoints were achieved only for A strains, but not for B strains. The investigational vaccine that met its efficacy objectives for adults 18 through 64 years of age in this study is CCI [37]
CCI

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.

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.[21,38] Vaccination remains an important means of reducing the risk of significant morbidity and mortality.[24] 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 mRNA vaccines designed to target influenza and the SARS-CoV-2 virus can demonstrate an acceptable safety and immunogenicity profile.

C5261001 is an ongoing Phase 1/2 study evaluating bivalent, trivalent, and quadrivalent influenza vaccines in combination with BNT162b2.

This study evaluated modRNA encoding influenza strains and BNT162b2 in combination up to a total modRNA dose of 90 µg. The data gathered to date in this study demonstrate that up to a total modRNA dose of 90 µg in a combination of either qIRV or tIRV with BNT162b2 is well tolerated and elicited immune responses against influenza and SARS-CoV-2 in participants aged 18 years and older. In C5261001 Substudy A, 60 participants 18 through 64 years of age have received a qIRV/BNT162b2 combination of 90 µg total modRNA. Thirty participants 18 through 64 years of age have received a qIRV/BNT162b2 combination of up to 60 µg total modRNA dose. C5261001 Substudy B is an ongoing Phase 1/2 study with additional safety and immunogenicity data being collected for both qIRV and tIRV in combination with BNT162b2.

Using these data supports progression to Phase 3 clinical development of a selected combination of CCI BNT162b2 and/or CCI BNT162b2 for adults 18 through 64 years of age up to CCI µg total modRNA.

Given that the WHO recommendation for the composition of influenza virus vaccines in the 2023-2024 northern hemisphere influenza season[1] includes both a quadrivalent and a trivalent vaccine without the B/Yamagata lineage, which has not been seen in circulation since March 2020,[2] the initial study design includes both a qIRV and a tIRV in combination with BNT162b2 previously tested in C5261001 Phase 1/2 up to CCI µg total modRNA. In February 2024, after the start of enrollment of this study, the WHO recommended that influenza vaccines for the 2024-2025 northern hemisphere influenza season be trivalent formulations without a B/Yamagata component.[4]

On 05 March 2024, the VRBPAC provided a recommendation for trivalent influenza vaccine formulations for the US,[5] CCI [redacted]. A third cohort (Cohort 3) will be added to evaluate the combined CCI /BNT162b2 (Omi XBB.1.5) compared to the licensed inactivated QIV CCI) when administered alone, the licensed COVID-19 vaccine when administered alone, and to CCI when

administered alone. This will allow for assessment of potential immune interference between the individual components of combined CCI BNT162b2 (Omi XBB.1.5).

CCI [redacted]

2.3. Benefit/Risk Assessment

The available safety and immunogenicity data from ongoing clinical trials and real-world effectiveness and safety data for BNT162b2, combined with available nonclinical data with BNT162 vaccines, and the data from nonclinical and clinical trials with CCI standalone and CCI when in combination with BNT162b2, 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.[39]

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): Selected CCI BNT162b2 (Omi XBB.1.5) and CCI BNT162b2 (Omi XBB.1.5)		
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. Other key risks identified for BNT162b2, and therefore for the combination vaccine candidates, are lymphadenopathy; hypersensitivity reactions, such as rash, pruritus, urticaria, angioedema, and anaphylaxis; and myocarditis and pericarditis.[40]	These are common adverse reactions seen with other vaccines,[41] 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.[29] 1-week follow-up reactogenicity data of 194 participants who received mIRV, bIRV, or qIRV in C4781001 Substudy A showed most events to be mild to moderate in severity, with the most common events being pain at the injection site, fatigue, and headache.	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time after each vaccination through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol. All study participants will be observed for at least 30 minutes after vaccination.
The safety and efficacy profile of a novel vaccine is not yet fully characterized.	Although CCI [redacted] 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, respectively, after vaccination. CCI [redacted] while the AESIs of myocarditis/pericarditis will be collected from vaccination through 6 weeks after vaccination. All participants will be observed for at least 30 minutes after vaccination.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): BNT162b2 (Omi XBB.1.5)		
This vaccine has the same modRNA platform and LNP formulation as the original BNT162b2; therefore, the safety profile is expected to be similar to that of BNT162b2, ie, local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain. Other key risks identified for BNT162b2 are lymphadenopathy; hypersensitivity reactions, such as rash, pruritus, urticaria, angioedema, and anaphylaxis; and myocarditis and pericarditis.[40]	These are common adverse reactions seen with other vaccines as well as the COVID-19 vaccine used in this study. 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.[29] 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	Local reactions and systemic events will be recorded using a reactogenicity e-diary to monitor local reactions and systemic events in real time after vaccination. AE and SAE reports will be collected from the signing of the ICD through 4 weeks and 6 months, respectively, after vaccination. CCI [redacted] while the AESIs of myocarditis/pericarditis will be collected from vaccination through 6 weeks after vaccination. Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.10.6.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients. Postauthorization safety data surveillance has confirmed the safety profile observed in Study C4591001 and has resulted in identification of some additional adverse reactions (risks) as noted in the SRSD.	
Study Intervention(s): QIV (CCI)		
Local and systemic reactions to the vaccines may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) following vaccination.	These are common adverse reactions seen with other vaccines.[42]	AE and SAE reports will be collected from the signing of the ICD through 4 weeks and 6 months, respectively, after vaccination. All study participants will be observed for at least 30 minutes after vaccination.
Study Intervention(s): CCI		
Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines as well as BNT162b2 (Omi XBB.1.5) used in this study.	Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately trained personnel will obtain the blood draw.

2.3.2. Benefit Assessment

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

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

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants as stated in Section 2.3.1, the potential risks identified in association with Arm A, Arm C, Arm E, Arm G, and Arm H are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Safety		
To describe the safety and tolerability of study interventions in healthy participants 18 through 64 years of age	• Local reactions (pain at the injection site, redness, and swelling) in the right deltoid only • 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 18 through 64 years of age receiving at least 1 dose of study intervention reporting: • Local reactions for up to 7 days following vaccination in the right deltoid 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
Immunogenicity		
To demonstrate that the HAI immune response elicited by CCI BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) (Cohort 2)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains (CCI) recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) • The difference in percentage of participants with seroconversion[a] to the seasonal strain CCI at 4 weeks after vaccination between participants who received CCI BNT162b2 (Omi XBB.1.5) and those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5)
To demonstrate that the SARS-CoV-2 immune response elicited by CCI BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV (Cohort 2)	• SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers	In evaluable immunogenicity participants: • GMR of SARS-CoV-2–neutralizing titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) compared to participants who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV • The difference in percentages of participants with seroresponse[b] to the SARS-CoV-2 Omicron (XBB.1.5) strain at 4 weeks after vaccination compared to participants who received CCI BNT162b2 (Omi XBB.1.5) and to those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
Immunogenicity		
To demonstrate that the HAI immune response elicited by CCI /BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by QIV alone (Cohort 3)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains CCI recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received QIV alone
To demonstrate that the SARS-CoV-2 immune response elicited by CCI /BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by BNT162b2 (Omi XBB.1.5) alone (Cohort 3)	• SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers	In evaluable immunogenicity participants: • GMR of SARS-CoV-2–neutralizing titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) alone
To demonstrate that the HAI immune response elicited by CCI /BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by CCI alone (Cohort 3)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains CCI recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received CCI alone
To demonstrate that the HAI immune response elicited by CCI /BNT162b2 (Omi XBB.1.5) is superior to that elicited by QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) (Cohort 2)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains (CCI) recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) • The difference in percentage of participants with seroconversion[a] to the seasonal strain CCI at 4 weeks after vaccination between participants who received CCI BNT162b2 (Omi XBB.1.5) and those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5)
Exploratory:	**Exploratory:**	**Exploratory:**
CCI [redacted]		

Objectives	Endpoints	Estimands
CCI		

Objectives	Endpoints	Estimands
CCI		

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

4. STUDY DESIGN

4.1. Design

This is a Phase 3 observer-blinded study to evaluate the safety, tolerability, and immunogenicity of selected CCI when administered in combination with BNT162b2 (Omi XBB.1.5) compared to a licensed inactivated QIV administered in the deltoid opposite to that used for administration of BNT162b2 (Omi XBB.1.5) in healthy adults 18 through 64 years of age. Additionally, the study will evaluate CCI administered in combination with BNT162b2 (Omi XBB.1.5) in comparison to standalone administration of QIV, CCI, or BNT162b2 (Omi XBB.1.5). The vaccine candidates are divided into cohorts, which will be studied in a staggered manner, as required by the clinical plan. This study will be observer-blinded (sponsor-blinded), where up to approximately 8550 total participants 18 through 64 years of age will be enrolled into 1 of 3 cohorts:

Cohort 1: Approximately 450 participants enrolled and randomized in a 2:1 ratio by site-based randomization to 1 of the following:

- **Arm A:** CCI /BNT162b2 (Omi XBB.1.5) administered in the right deltoid and placebo administered in the left deltoid, concurrently.
- **Arm B:** 30 µg BNT162b2 (Omi XBB.1.5) administered in the right deltoid and licensed QIV CCI) administered in the left deltoid, concurrently.

Enrollment of Cohort 1 will be paused in the IRT after the randomization of approximately 450 participants into Cohort 1. Safety data (including e-diary reactogenicity data, SAEs, AEs, and AESIs) of approximately 450 vaccinated participants will be evaluated by the EDMC after 60 days CCI

CCI

Cohort 2: Approximately 4500 participants enrolled and randomized in a 2:1 ratio by site-based randomization to 1 of the following:

- **Arm C:** CCI /BNT162b2 (Omi XBB.1.5) administered in the right deltoid and placebo administered in the left deltoid, concurrently.
- **Arm D:** 30 µg BNT162b2 (Omi XBB.1.5) administered in the right deltoid and licensed QIV (CCI) administered in the left deltoid, concurrently.

Cohort 3: Approximately 3600 participants 18 through 64 years of age will be enrolled and randomized in a 2:2:1:1 ratio by site-based randomization to 1 of the following:

- **Arm E:** CCI /BNT162b2 (Omi XBB.1.5) administered in the right deltoid.
- **Arm F:** 30 µg BNT162b2 (Omi XBB.1.5) administered in the right deltoid.
- **Arm G:** licensed QIV (CCI) administered in the right deltoid.
- **Arm H:** CCI administered in the right deltoid.

See Section 6.1.1 for additional details on study intervention administration in all cohorts. The CCI dose levels to be used in combination with BNT162b2 (Omi XBB.1.5) this study are based on Phase 1/2 safety and immunogenicity data and are detailed in Section 6.1. CCI .

Prespecified local reaction and systemic event data will be collected in an e-diary during the 7 days, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution), as well as any medication taken during this period to treat any of these symptoms. Blood samples of approximately 20 mL will be collected for immunogenicity assessments prior to vaccination and at 4 weeks and 6 months after vaccination.

CCI .

Following vaccination, AEs will be collected from informed consent signing through Visit 2, and SAEs will be collected from informed consent signing through Visit 3. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures will also be collected. For the collection of AESIs, refer to Section 8.4.8 for further details. This study will use an EDMC; refer to Section 10.1.5.1 for further details.

4.2. Scientific Rationale for Study Design

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

4.2.1. Diversity of Study Population

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

- Selecting sites that have access to diverse participants within their locales.

- Educating sites about the importance of increasing diversity in clinical trials and Pfizer's commitment to diversity and inclusion.

- Use of real-world data to target outreach and potential referring physicians.

Continual monitoring of diverse enrollment to identify additional opportunities to include diverse populations.

4.2.2. Choice of Contraception/Barrier Requirements

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 10.4).

4.3. Justification for Dose

4.3.1. Monovalent BNT162b2 (Omi XBB.1.5)

The 30-µg dose level of BNT162b2 was shown to be effective and has been approved in multiple countries worldwide in both the original and bivalent formulations.

4.3.2. CCI /BNT162b2 (Omi XBB.1.5) and CCI /BNT162b2 (Omi XBB.1.5)

Based on the safety data in Study C5261001 Substudy A for participants exposed to up to 90 µg total modRNA dose, all combinations of qIRV/BNT162b2 are well tolerated, with mainly mild to moderate local reactions and systemic events, consistent with the safety data for BNT162b2 and qIRV administered alone. Based on C5261001 immunogenicity data from both Substudy A and Substudy B, up to 90 µg total modRNA doses produced an immune response, and dose levels of the combination CCI BNT162b2 and the combination CCI /BNT162b2 were selected to be evaluated in this study. Refer to Section 6.1 and the IPM for further details.

CCI

In C4781004, the CCI µg qIRV CCI met its study objectives for the demonstration of efficacy in the prevention of laboratory-confirmed influenza.[37] CCI

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed the last visit of the study.

5. STUDY POPULATION

This section is applicable to all cohorts.

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

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

5.1. Inclusion Criteria

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

Age and Sex:

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

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

Disease Characteristics:

No applicable.

Other Inclusion Criteria:

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

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

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

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

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

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

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.

10. Vaccination with any investigational or licensed COVID-19 vaccine within 6 months (175 days) before study intervention administration.

Prior/Concurrent Clinical Study Experience:

11. 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:

No applicable.

Other Exclusion Criteria:

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

5.3. Lifestyle Considerations

5.3.1. Contraception

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

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

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

as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

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

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

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

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

5.5. Screen Failures

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

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

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 investigational product.

6.1. Study Intervention(s) Administered

Cohort 1

- **Arm A:** CCI BNT162b2 (Omi XBB.1.5) and normal saline placebo
- **Arm B:** QIV (CCI) and 30 µg BNT162b2 (Omi XBB.1.5)

Cohort 2

- **Arm C:** CCI BNT162b2 (Omi XBB.1.5) and normal saline placebo
- **Arm D:** QIV CCI) and 30 µg BNT162b2 (Omi XBB.1.5)

Cohort 3

- **Arm E:** CCI /BNT162b2 (Omi XBB.1.5)
- **Arm F:** 30 µg BNT162b2 (Omi XBB.1.5)
- **Arm G:** QIV (CCI)
- **Arm H:** CCI

Study Intervention(s)						
Intervention Name	CCI BNT162b2 (Omi XBB.1.5)	CCI BNT162b2 (Omi XBB.1.5)	QIV CCI	CCI	BNT162b2 (Omi XBB.1.5)	Normal saline placebo
Type	mRNA vaccine	mRNA vaccine	Vaccine	Vaccine	mRNA vaccine	Placebo
Use	Experimental	Experimental	Comparator	Experimental (all cohorts) Comparator (Cohort 3 only)	Comparator	Placebo
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP
Dose Formulation	modRNA	modRNA	Suspension for injection	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	µg	µg	60 µg HA per 0.5-mL dose	µg	30 µg	N/A
Dosage Level(s)	CCI µg BNT162b2 (Omi XBB.1.5)	CCI	60 µg	CCI	30 µg BNT162b2 (Omi XBB.1.5)	N/A

Study Intervention(s)						
		CCI µg BNT162b2 (Omi XBB.1.5)				
Targeted Influenza Strains	As recommended by WHO for cell culture– or recombinant-based vaccines (2023-2024 northern hemisphere influenza season)[a]				N/A	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided as either a PFS or a glass/plastic vial as open-label supply.	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.

a. For CCI [redacted] [1]

6.1.1. Administration

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

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

Study intervention administration details will be recorded on the CRF.

Participants will receive 2 injections at Visit 1 in Cohort 1 and Cohort 2 and will receive 1 injection at Visit 1 in Cohort 3 as randomized in accordance with the SoA. Study intervention should be administered intramuscularly into the deltoid muscle of the appropriate arm as detailed in Table 1 and Table 2. Study intervention will be administered only by an unblinded administrator.

Table 1. Study Intervention Schedule: Cohort 1 and Cohort 2

Cohort	Study Arm	Right Deltoid[a]	Left Deltoid
1	A	CCI BNT162b2 (Omi XBB.1.5)	Placebo
	B	30 µg BNT162b2 (Omi XBB.1.5)	60 µg QIV (CCI)
2	C	CCI BNT162b2 (Omi XBB.1.5)	Placebo
	D	30 µg BNT162b2 (Omi XBB.1.5)	60 µg QIV CCI

a. Local reactions will be assessed at the injection site on the right deltoid.

Table 2. Study Intervention Schedule: Cohort 3

Cohort	Study Arm	Right Deltoid[a]
3	E	CCI BNT162b2 (Omi XBB.1.5)
	F	30 µg BNT162b2 (Omi XBB.1.5)
	G	60 µg QIV (CCI)
	H	CCI

a. Local reactions will be assessed at the injection site on the right deltoid.

6.1.2. Medical Devices

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

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

6.2. Preparation, Handling, Storage, and Accountability

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

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

3. 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.

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

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

6. 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.

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

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

6.2.1. Preparation and Dispensing

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

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

6.3. Assignment to Study Intervention

Allocation (randomization) of participants to study arms will proceed through the use of an IRT system (IWR). The unblinded site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned study intervention.* The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. Confirmation report must be stored in the site's files.

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

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

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

Enrollment of Cohort 1 will be controlled in the following fashion: Randomization in the IRT will be paused after enrollment of approximately 450 participants into Cohort 1. After the EDMC has reviewed the safety data from these participants and agreed to continue the study, the IRT will be released to allow the enrollment of the remaining participants into Cohort 1. CCI [redacted] The enrollment of Cohort 2 and Cohort 3 will not involve an enrollment pause in the IRT.

6.4. Blinding

This is an observer-blinded study.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

The study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator and investigator staff, will be blinded to assignment of study intervention. In particular, the individuals who evaluate participant safety will be blinded. Because there are differences in physical appearance of the study interventions, these will be administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

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

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

6.4.3. Blinding of the Sponsor

The majority of sponsor staff will be blinded to study intervention allocation during the enrollment. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor/Pfizer staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s) who are not direct members of the study team and will not participate in any other study-related activities will review unblinded protocol deviations.
- A team supporting interactions with, and analyses for, the EDMC (see Section 10.1.5.1) will be unblinded.
- An unblinded submissions team may be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. A separate group of team members will remain blinded and continue supporting the blinded conduct of the study after such an analysis.

6.4.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's study intervention assignment unless this could delay further management of the participant. If a participant's study intervention assignment is

unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

6.5. 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 follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.

6.9. Prior and Concomitant Therapy

This section is applicable to all cohorts. The following concomitant medications and vaccinations will be recorded in the CRF:

- Ongoing medications if taken, will be recorded and include start date, name of the medication, dose, unit, route, and frequency at Visit 1.
- All prior receipt of any COVID-19 vaccines.
- Date of licensed or investigational influenza vaccine within the 3 years prior to enrollment.
- Any vaccinations received from 28 days prior to Visit 1 until the last visit (Visit 3).
- Prohibited medications listed in Section 6.9.1, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.
- Details of any concomitant medication taken to treat any prespecified local or systemic reactogenicity symptoms reported in the e-diary will be collected.

6.9.1. Prohibited During the Study

This section is applicable to both all cohorts.

Unless considered medically necessary, the following interventions are prohibited during the study, and receipt of these interventions will result in exclusion from the relevant analysis (depending on timing of prohibited vaccination or medication use) of immunogenicity data in the per-protocol analysis:

- Vaccines other than study intervention administered within 28 days before and 28 days after study vaccination at Visit 1.
- Receipt of any other (nonstudy) COVID-19 vaccine from enrollment throughout the entire study.
- Receipt of any other (nonstudy) seasonal influenza vaccine from enrollment throughout the entire study.

Note: Should a participant experience a change in health status that places that participant at increased risk of severe influenza or COVID-19 complications, and therefore request to receive licensed influenza and/or COVID-19 vaccine during study participation, the following steps should be taken. The health status change will be documented as an AE, the receipt of the licensed vaccines will be documented as a concomitant vaccine, the original vaccine assignment will not be unblinded for the purposes of decision making as to which licensed vaccine(s) to receive, and the participant will be asked to continue all study assessments through the final visit with the exception of further blood sampling for immunogenicity testing. The receipt of the licensed influenza and/or COVID-19 vaccine will be recorded as a protocol deviation.

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

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

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

- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies, 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 prior to study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.9.2. Permitted During the Study

This section is applicable to all cohorts.

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

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

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Reactogenicity event;
- AEs;
- Participant request;
- Investigator request;
- Select protocol deviations

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

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or postvaccination

study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the

test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

The total blood sampling volume for individual participants in this study is approximately 60 mL, or [redacted] The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

8.1.1. Telehealth Visits

Any participants who have scheduled blood draws discontinued* may be followed for safety at Visit 2 (Week 4) and Visit 3 (Month 6) via telehealth visits. Note: Visit 1 (Day 1) must remain as an in-person visit to the site.

> *For example, blood draws discontinued because the participant no longer meets the eligibility criteria.

General Requirements:

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

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

8.2. Immunogenicity Assessments

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

Cohort 1

- HAI titers (from HAI based on [redacted] derived virus) for the matched seasonal strains ([redacted]) recommended by WHO.

- SARS-CoV-2 neutralization assays (Omi XBB.1.5).

Cohort 2

- HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains (CCI) recommended by WHO.
- SARS-CoV-2 neutralization assays (Omi XBB.1.5).

Cohort 3

- HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains (CCI) recommended by WHO.
- SARS-CoV-2 neutralization assays (Omi XBB.1.5).

8.2.2. Biological Samples

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

No testing of the participant's DNA will be performed, CCI [redacted]

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

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

8.3.2. Vital Signs

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

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

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

8.3.3. Clinical Safety Laboratory Assessments

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

8.3.4. Electronic Diary

All participants will be required to complete a reactogenicity e-diary after vaccination given at Visit 1, through an application installed on a provisioned device or on the participant's own personal device. All participants will be asked to monitor and record local reactions,

systemic events, and use of antipyretic medication for 7 days, or longer for ongoing symptoms, from the day of administration of the study intervention given at Visit 1. The reactogenicity e-diary allows recording of these assessments each day, thus providing the accurate representation of the participant's experience. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

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

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

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

8.3.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[41]

8.3.4.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. Local reactions will be assessed at the injection site on the **right deltoid** only after vaccinations given at Visit 1.

Note: Any local reaction occurring at the injection site on the **left deltoid** will be collected in the CRF as an AE.

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

Participants will be provided with a measuring device. Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized

during analysis as absent, mild, moderate, or severe based on the grading scale in Table 3. 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 3.

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 3. Local Reaction Grading Scale

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

8.3.4.3. Systemic Events

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 4.

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

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

Table 4. 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

8.3.4.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary daily for 7 days or longer following vaccination (where Day 1 is the day of vaccination). It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 5 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, to confirm compliance with the thermometer instructions given, and to determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor.

Fevers >40.0°C (>104.0°F) will be collected on the CRF.

Table 5. Scale for Fever

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

8.3.4.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the 7-day reporting period or longer for ongoing symptoms. Medication use indicated in the e-diary should be followed up by the site to transcribe details of the medication (as per Section 6.9) into the CRF.

8.3.5. 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 SoA, immediately before the administration of each dose of study intervention. A negative pregnancy test result will be required prior to receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

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

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

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

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

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

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 2 for AEs and Visit 3 for SAEs.

Please refer to Section 8.4.8 for the time period for reporting AESIs.

Additionally:

- Any AE occurring up to 48 hours after any subsequent blood draws and deemed related to study procedures must be recorded in the CRF.
- Any local reactogenicity event that occurs in the **left deltoid** is to be reported as an AE in the CRF.

SAEs will be collected from the time the participant provides informed consent through and including Visit 3. Deaths, pneumonia, and hospitalizations will be recorded for the entire study duration, as AEs/SAEs as appropriate.

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

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

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

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

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

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

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

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

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

Not applicable.

8.4.8. Adverse Events of Special Interest

The following events are protocol-specified AESIs and are collected from vaccination through 6 months after vaccination unless otherwise specified:

CCI

- Confirmed diagnosis of myocarditis or pericarditis occurring after Visit 1 through 6 weeks after vaccination. See Section 8.10.6.

- Potential menstrual cycle disturbances occurring after Visit 1 through 6 months after vaccination. See Section 8.10.7.

Protocol-specified AESIs are examined as part of routine safety data review and signal detection processes and procedures throughout the clinical trial. 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 protocol-specified AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported on the Vaccine SAE Report Form or via PSSA.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

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

The definition of a medical device deficiency can be found in Appendix 9.

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

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

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

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

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

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

8.4.9.2. Follow-Up of Medical Device Deficiencies

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

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

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

8.4.9.3. Regulatory Reporting Requirements for Device Deficiencies

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

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

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

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

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

8.4.10. Vaccination Errors

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

Vaccination errors are recorded and reported as follows:

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

Vaccination errors include:

- Vaccination errors involving participant exposure to the study intervention;

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

- The administration of expired study intervention;

- The administration of an incorrect study intervention;

- The administration of an incorrect dosage;

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

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

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

8.6.1. Specified Genetics

CCI [redacted]

See Section 10.5 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.6.1.1. Use/Analysis of DNA

Refer to Section 10.5.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Refer to Section 8.2.

8.9. Health Economics

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

8.10. Study Procedures

This section is applicable to all cohorts.

8.10.1. Visit 1 – Vaccination (Day 1)

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

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

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including age in years, sex, race, and ethnicity).
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken as described in Section 6.
- On the day of and prior to study intervention administration, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record findings on the medical history CRF.
- Measure the participant's height and weight.
- On the day of and prior to study intervention administration, measure the participant's oral temperature.
- Record nonstudy vaccinations and prior receipt of any licensed or investigational COVID-19 or influenza vaccine as described in Section 6.9.
- On the day of and prior to study intervention administration, perform urine pregnancy test on WOCBP as described in Section 8.3.5.
- If applicable, discuss contraceptive use as described in Section 10.4.4.
- On the day of and prior to study intervention administration, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and prior to study intervention administration, ensure that the participant meets none of the temporary delay criteria as described in Section 5.4.
- Collect a blood sample (approximately 20 mL), before administration of study intervention, for immunogenicity assessment.

CCI [redacted]

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

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the appropriate arm as detailed in Section 6.1.1. Please refer to the IPM for further instruction on this process.

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

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

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

- Issue a measuring device to measure local reactions at the right arm injection site and a thermometer for recording daily temperatures; provide instructions on their use.

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the right arm injection site.

  - Any severe systemic event.

- Record AEs, SAEs, and AESIs as described in Section 8.4.

  - Remind participants to inform the study staff of any AEs and SAEs that occur for the duration of the trial as described in Section 8.4

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

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.6).

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online and records the assessment in the CRF following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.10.2. Visit 1A – 1-Week Follow-Up CCI [redacted] – 6 to 8 Days After Visit 1

CCI [redacted] This visit must be completed at a site.

- Record AEs, SAEs, and AESIs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 6.9.
- Record prohibited medication use as described in Section 6.9.1.
- If applicable, discuss contraceptive use as described in Section 10.4.4

CCI [redacted]

- Review the participant's reactogenicity e-diary data and record the assessment in the CRF. Assess compliance, any medically attended events (including hospitalizations), and collect stop dates for any symptoms/medications ongoing on the last day of the e-diary collection period in the CRF. For symptoms still ongoing, continue to follow up until resolution, and document and record stop dates in the CRF.
- Record reactogenicity medication used as described in Section 6.9.
- Remind participants to inform the study staff of any AEs and SAEs that occur for the duration of the trial as described in Section 8.4
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.6).

- 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.

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

Note: Visit 2 may be performed as a telehealth visit if the participant had blood draws discontinued.

- Record AEs, SAEs, and AESIs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 6.9.
- Record prohibited medication use as described in Section 6.9.1.
- If applicable, discuss contraceptive use as described in Section 10.4.4.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.

CCI

- Review the participant's reactogenicity e-diary data and record assessment in the CRF. Assess compliance, any medically attended events (including hospitalizations), and collect stop dates for any symptoms/medications ongoing on the last day of the e-diary collection period in the CRF. For symptoms still ongoing, continue to follow up until resolution, and document and record stop dates in the CRF.
- Record reactogenicity medication used as described in Section 6.9.
- Remind participants to inform the study staff of any AEs and SAEs that occur for the duration of the trial as described in Section 8.4
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.4.

8.10.4. Visit 3 – 6-Month Follow-Up Visit (After Vaccination) – 168 to 196 Days After Visit 1

Note: Visit 3 may be performed as a telehealth visit if the participant had blood draws discontinued.

- Record SAEs and AESIs as described in Section 8.4.
- Record nonstudy vaccinations as described in Section 6.9.
- Record prohibited medication use as described in Section 6.9.1.
- Collect a blood sample of approximately 20 mL for immunogenicity testing.

CCI

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.4.

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

If a Grade 3 local reaction in the right arm (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever (Section 8.3.4.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction in the right arm (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever (Section 8.3.4.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets Grade 4 criteria.

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

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

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

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be 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 in the right arm (if present).
- Measure minimum and maximum diameters of swelling in the right arm (if present).
- Assess injection site pain in the right arm (if present) in accordance with the grades provided in Section 8.3.4.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.3.4.3.
- Assess for other findings associated with the reaction and record these on the CRF if appropriate.

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

Note: Any left arm reactogenicity event should be collected in the CRF on the AE log page.

8.10.6. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports symptoms (including, but not limited to, acute chest pain, shortness of breath, and palpitations) will be evaluated at the site **preferably within 48 hours but no more than 72 hours of onset** (if the participant is medically stable and not otherwise seeking medical attention).

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

- ECG and
- Measurement of the troponin level.

Any study participant with clinical findings noted within 6 weeks after study vaccination and whom the investigator assesses as clinically suspicious for myocarditis or pericarditis must be evaluated by a cardiologist.

As part of the **cardiologist** evaluation, the following should also be performed in addition to other appropriate clinical tests to elucidate if the participant has experienced myocarditis or pericarditis:

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

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF. Any diagnosis made (myocarditis, pericarditis, or other) should be recorded as an AE. Refer also to Section 8.4.8.

8.10.7. Additional Procedures for Monitoring of Potential Menstrual Cycle Disturbances

Any female study participant who reports any symptoms that may indicate a disturbance of their normal menstrual cycle (including, but not exclusively, heavy menstrual bleeding, amenorrhea, irregular periods) following receipt of study intervention until 6 months after the last vaccination should be specifically evaluated by the investigator. Details of the symptoms, menstrual history, and results of any investigations performed will be recorded in the CRF.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a 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

Two immunogenicity primary objectives and4 immunogenicity secondary objectives have been defined for this study. The immunogenicity primary (Cohort 2) and secondary (Cohort 3) objectives involve a demonstration of NI of the immune responses measured 4 weeks after study intervention administration, and the immunogenicity secondary (Cohort 2) objective involves a demonstration of superiority of the immune responses measured 4 weeks after study intervention administration, as detailed below.

The immunogenicity primary objectives (Cohort 2) are to demonstrate NI of the immune response to CCI /BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV for all targeted strains (seasonal strains CCI] recommended by WHO) and the SARS-CoV-2 Omicron XBB.1.5 strain.

The first immunogenicity secondary objective (Cohort 3) is to demonstrate NI of the HAI immune response for the matched seasonal influenza strains recommended by WHO ([CCI] elicited by CCI /BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to QIV alone.

The second immunogenicity secondary objective (Cohort 3) is to demonstrate NI of the SARS-CoV-2 immune response elicited by CCI BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to BNT162b2 (Omi XBB.1.5) alone.

The third immunogenicity secondary objective (Cohort 3) is to demonstrate NI of the HAI immune response for the matched seasonal influenza strains recommended by WHO (CCI elicited by CCI BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to CCI alone.

The fourth immunogenicity secondary objective (Cohort 2) is to demonstrate superiority of the immune response to CCI /BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV for all targeted strains (seasonal strains CCI recommended by WHO).

For evaluation of the immunogenicity primary objectives (Cohort 2), 2 statistical hypotheses for each targeted strain will be defined as described below:

$H_{01}: \ln(\mu_1) - \ln(\mu_2) \leq \ln$ CCI),

where ln(CCI) corresponds to a CCI margin for NI, and μ_1 and μ_2 are the GMTs from Arm C and Arm D, respectively, measured at 4 weeks after vaccination.

$H_{02}: \pi_1 - \pi_2 \leq$ CCI %,

where π_1 and π_2 are the proportions of participants achieving seroconversion or seroresponse at 4 weeks after vaccination for Arm C and Arm D, respectively.

For evaluation of immunogenicity secondary objectives (Cohort 3), 1 statistical hypothesis for each target strain will be defined as described below:

$H_{01}: \ln(\mu_1) - \ln(\mu_2) \leq \ln($CCI ,

where ln(CCI) corresponds to a CCI margin for NI, and μ_1 and μ_2 are the GMTs in Arm E and the corresponding comparative (Arm F and Arm G) and experimental (Arm H) vaccine groups, respectively, measured 4 weeks after vaccination.

For evaluation of the immunogenicity secondary objective (Cohort 2), 2 statistical hypotheses for each targeted seasonal strain ([CCI recommended by WHO) will be defined as described below:

$H_{01}: \ln(\mu_1) - \ln(\mu_2) \leq \ln($CCI ,

where ln(CCI corresponds to a CCI margin for superiority, and μ_1 and μ_2 are the GMTs from Arm C and Arm D, respectively, measured at 4 weeks after vaccination.

$H_{02}: \pi_1 - \pi_2 \leq$ CCI %,

where π_1 and π_2 are the proportions of participants achieving seroconversion at 4 weeks after vaccination for Arm C and Arm D, respectively.

For each strain, NI based on GMT will be declared if the lower limit of the 2-sided 95% CI for the GMR is CCI ; NI based on seroconversion or seroresponse (Cohort 2 only) will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants achieving seroconversion or seroresponse is greater than CCI %; superiority (Cohort 2 only) based on GMT will be declared if the lower limit of the 2 sided 95% CI for the GMR is CCI superiority based on seroconversion (Cohort 2 only) will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants achieving seroconversion is CCI
CCI

9.1.1. Estimands

The estimands corresponding to the primary and secondary objectives are described in the table in Section 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. The estimands addresses the objective of estimating the maximum potential difference between 2 study arms of the target population, since the impact of noncompliance is likely to diminish the observed difference between the 2 compared study arms. Missing immunogenicity results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analyses. Data handling for immunogenicity following onset of infection for participants who have influenza or COVID-19 will be outlined in the SAP.

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.

9.1.2. Multiplicity Adjustment

Hypothesis testing of the objectives for Cohort 2 (2 immunogenicity primary objectives and the fourth secondary objective) will be evaluated independently from that of Cohort 3 (3 immunogenicity secondary objectives) without applying any multiplicity adjustment . CCI

Within Cohort 2, the immunogenicity primary objectives and the fourth secondary objective will be evaluated sequentially. The immunogenicity primary endpoints/estimands are considered coprimary. There are CCI hypothesis tests (CCI) for the immunogenicity primary NI objectives (CCI BNT162b2 [Omi XBB.1.5] vs BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV), with 2 statistical hypotheses for each of the CCI targeted influenza and SARS-CoV-2 strains. Each hypothesis will be tested at a 1-sided alpha level of 0.025. The immunogenicity primary objectives will be achieved if NI is met for all CCI statistical hypotheses. After the immunogenicity primary NI objectives (Cohort 2) are established, the CCI statistical hypotheses for the fourth secondary objective (Cohort 2) will be tested sequentially in the following order of CCI seasonal influenza strains: CCI and the hypothesis will be tested first based on GMR and then based on the seroconversion rate for each strain. Therefore, the overall type I error rate within Cohort 2 is fully controlled.

Within Cohort 3, the 3 immunogenicity secondary objectives will be evaluated sequentially in the following order: comparing CCI /BNT162b2 [Omi XBB.1.5] with QIV for CCI targeted influenza strains, CCI /BNT162b2 [Omi XBB.1.5] with BNT162b2 [Omi XBB.1.5] for the SARS-CoV-2 Omicron XBB.1.5 strain, and CCI /BNT162b2 [Omi XBB.1.5] with CCI for CCI targeted influenza strains. There are CCI hypothesis tests for the immunogenicity secondary NI objectives CCI /BNT162b2 [Omi XBB.1.5] vs QIV for CCI targeted influenza strains, 1 for CCI /BNT162b2 [Omi XBB.1.5] vs BNT162b2 [Omi XBB.1.5] for the SARS-CoV-2 Omicron XBB.1.5 strain, and CCI /BNT162b2 [Omi XBB.1.5] vs CCI for CCI targeted influenza strains). Each hypothesis will be tested at a 1-sided alpha level of 0.025. For objectives involving hypotheses for CCI influenza strains, all CCI hypotheses within the objective must be established before assessing the next objective in the sequence. Therefore, the overall type I error within Cohort 3 is fully controlled.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Screened	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All randomized 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. Participants will be grouped according to the vaccine as randomized in the analysis based on the evaluable immunogenicity population.
mITT immunogenicity	All randomized participants who receive the study intervention and have at least 1 valid and determinate assay result after vaccination. Participants will be grouped according to the vaccine as randomized in the analysis based on the mITT immunogenicity population.

Participant Analysis Set	Description
Safety	All participants who receive the study intervention. Participants will be grouped according to the vaccine as administered in the analysis based on the safety population.

9.3. Statistical Analyses

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

9.3.1. General Considerations

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

For all the immunogenicity endpoints, the analysis will be primarily based on the evaluable immunogenicity population. An additional analysis will be performed based on the mITT immunogenicity population if there is a large enough difference in the number of participants included between the mITT and the evaluable immunogenicity populations.

9.3.1.1. Analysis for Binary Data

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

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

For the between-group difference, the 2-sided 95% CI will be calculated using the Miettinen and Nurminen method.

Three-Tier Approach for AE Summary

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers:

1. Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; there is no Tier 1 event identified for the study interventions at this stage.

2. Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 study arm reporting the event.

3. Tier 3 events are those that are neither Tier 1 nor Tier 2 events.

- For both Tier 1 (if any are identified later) and Tier 2 events, the 95% CIs for the difference in percentage of participants reporting the events between Arm A and Arm B and between Arm C and Arm D will be calculated using the Miettinen and Nurminen method.

- In addition, for Tier 1 events (if any are identified later), the asymptotic p-values will also be presented for the difference in percentage of participants reporting the events between Arm A and Arm B and between Arm C and Arm D, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed.

- Descriptive summary statistics will be provided for Tier 3 events for each study arm.

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.

9.3.1.3. 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.

9.3.1.4. Geometric Mean Ratio

Unadjusted GMR

The unadjusted GMR will be calculated as the difference in the means of logarithmically transformed assay results between 2 vaccine groups and exponentiating the difference. The 2-sided 95% CI will be obtained by exponentiating the limits of the CI for the mean difference of the logarithmically transformed assay results based on the t distribution.

Model-based GMR

The model-based GMR and associated 95% CI will be calculated by exponentiating the difference in LS means and the corresponding CIs based on the analysis of logarithmically transformed assay results using a linear regression model that includes the baseline neutralizing titer, age, and vaccine group as covariates.

9.3.1.5. 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 no missing values at both time points.

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

9.3.1.5.1. Reverse Cumulative Distribution Curves

Empirical RCDCs will be plotted as a step function of the proportion of participants with the assay results equal to or exceeding a specified value over the full range of the observed assay results.

9.3.2. Primary Endpoints/Estimands Analysis

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group within each cohort. Local reactions and systemic events from Day 1 through Day 7 after each vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentage of participants with the indicated endpoint and the associated 2-sided 95% CIs based on Clopper-Pearson method. • AEs and SAEs will be categorized according to MedDRA terms. Counts, percentage, and associated 2-sided 95% CIs based on Clopper-Pearson method of AEs from vaccination (Day 1) through 4 weeks after vaccination, and SAEs from vaccination (Day 1) through 6 months after vaccination will be provided for each vaccine group within each cohort. • The safety data are summarized within each cohort but may also be summarized descriptively across cohorts as specified in the SAP.
Immunogenicity (Cohort 2)	• GMR of HAI titers for each matched seasonal strain [CCI]) at 4 weeks after study vaccination in participants who received [CCI] BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV.

Endpoint	Statistical Analysis Methods
	• The difference in percentages of participants with seroconversion to the seasonal strain (CCI [redacted] at 4 weeks after study vaccination between participants who received CCI [redacted] BNT162b2 (Omi XBB.1.5) and those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV. • GMR of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers at 4 weeks after study vaccination in participants who received CCI [redacted] BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV. • The difference in percentages of participants with seroresponse to SARS-CoV-2 Omicron (XBB.1.5) strain at 4 weeks after study vaccination between participants who received CCI [redacted] BNT162b2 (Omi XBB.1.5) and those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV. • GMRs and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.4 Unadjusted GMRs will be the primary approach. Adjusted GMRs will also be summarized as supportive. • The differences in percentage of participants with seroconversion/seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method in Section 9.3.1.1.

9.3.3. Secondary Endpoints/Estimands Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity (Cohort 3)	• GMR of HAI titers for each matched seasonal strain (CCI [redacted]) at 4 weeks after vaccination for participants who received CCI [redacted] BNT162b2 (Omi XBB.1.5) to those who received QIV alone. • GMR of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers at 4 weeks after vaccination for participants who received CCI [redacted] BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) alone.

Endpoint	Statistical Analysis Methods
	• GMR of HAI titers for each matched seasonal strain (CCI at 4 weeks after vaccination for participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received CCI alone. • GMRs and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.4 Unadjusted GMR will be the primary approach. Adjusted GMRs will also be summarized as supportive.
Immunogenicity (Cohort 2)	• GMR of HAI titers for each matched seasonal strain (CCI at 4 weeks after study vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV. • The difference in percentages of participants with seroconversion to the seasonal strain (CCI) at 4 weeks after study vaccination between participants who received CCI /BNT162b2 (Omi XBB.1.5) and those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV. • The same analyses and estimands as the immunogenicity primary objective for HAI response.

9.3.4. Exploratory Endpoints Analysis

Endpoint	Statistical Analysis Methods
CCI	

Endpoint	Statistical Analysis Methods
CCI	[redacted]

CCI [redacted]

9.3.5. Other Safety Analyses

All safety analyses (including reactogenicity and unsolicited AEs) are performed on the safety population.

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below.

9.4.1. Analysis Timing

Statistical analyses will be carried out when data are available for each cohort as specified below:

- Safety and immunogenicity data through 4 weeks after vaccination after all participants complete 4 weeks after vaccination (for the respective cohort).
- Safety, immunogenicity, and other data through 6 months after vaccination (for the respective cohort).

Additional analyses may be conducted if required for regulatory purposes after the immunogenicity primary or secondary hypotheses for the respective cohort have been evaluated. The study team will remain blinded through end of the study as per Section 6.4, as the analysis prior to the final analysis at end of the study will be performed by a separate unblinded statistical team. The investigator site staff will remain blinded to participant study arm until the last participant completes the final visit. Laboratory personnel performing the assays will remain blinded until all assays are completed.

9.5. Sample Size Determination

9.5.1. Immunogenicity

The sample size of up to 8550 participants was determined to generate an adequate safety database for licensure and with sufficient statistical power for achieving immunogenicity primary (Cohort 2) and secondary (Cohort 3) objectives. In Cohort 2, approximately 4500 participants will be randomized in a 2:1 ratio to receive either CCI BNT162b2 (Omi XBB.1.5) or coadministered QIV and BNT162b2 (Omi XBB.1.5). In Cohort 3, approximately 3600 participants will be randomized in a 2:2:1:1 ratio to receive either CCI BNT162b2 (Omi XBB.1.5), BNT162b2 (Omi XBB.1.5), QIV, or CCI

In Cohort 2, NI of the immune response elicited by the combination vaccine (CCI BNT162b2 [Omi XBB.1.5]) to coadministration of QIV and BNT162b2 (Omi XBB.1.5) will be assessed based on HAI antibody GMRs and/or SARS-CoV-2 GMR using a CCI margin and difference of HAI antibody seroconversion rates and/or SARS-CoV-2 seroresponse rates using a CCI % margin.

In Cohort 3, NI of the immune response elicited by the combination vaccine CCI BNT162b2 [Omi XBB.1.5]) to BNT162b2 (Omi XBB.1.5) alone will be assessed based on SARS-CoV-2 Omicron (XBB.1.5) antibody GMR using CCI margin; NI of the immune response elicited by the combination vaccine CCI /BNT162b2 [Omi XBB.1.5]) to QIV or CCI alone will be assessed based on HAI antibody GMRs using CCI margin.

For the immunogenicity primary objectives related to the demonstration of NI of the immune responses elicited by CCI /BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to BNT162b2 (Omi XBB.1.5) administered concurrently with QIV , all enrolled participants will be tested for SARS-CoV-2 Omicron XBB.1.5–neutralizing titers and a random subset of

approximately 3000 participants (2000 from CCI /BNT162b2[Omi XBB.1.5] group and 1000 from BNT162b2 [Omi XBB.1.5] and QIV coadministration group) will be tested for HAI titers. The overall power to demonstrate NI across the endpoints under various assumptions for GMRs and differences in percentage of participants achieving seroconversion or seroresponse is presented in Table 6. CCI [redacted]

Similarly, the power related to the demonstration of NI of the immune response elicited by CCI /BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to BNT162b2 (Omi XBB.1.5), CCI and QIV alone for given assumptions is presented in Table 7.

Table 6. Power Analysis for Noninferiority Assessment (Cohort 2: Immunogenicity Primary Objectives)

Assumed GMR CCI BNT162b2 to QIV+BNT162b2)		Assumed Difference of Seroresponse/Seroconversion Rates CCI /BNT162b2 Minus QIV+BNT162b2)		Evaluable Participants/Study Arm				Power[a]
SARS-CoV-2 Omicron XBB.1.5–neutralizing titers	HAI titers for seasonal influenza strains	SARS-CoV-2 Omicron XBB.1.5–neutralizing titers	HAI titers for seasonal influenza strains	SARS-CoV-2 Omicron XBB.1.5–neutralizing titers		HAI titers for seasonal influenza strains		
				CCI BNT162b2 (Omi XBB.1.5)	QIV+BNT162b2	CCI BNT162b2 (Omi XBB.1.5)	QIV+BNT162b2	
CCI [redacted]								

Table 7. Power Analysis for Noninferiority Assessment (Cohort 3: Immunogenicity Secondary Objectives)

Assumed GMR		Evaluable Participants/Study Arm		Power
SARS-CoV-2 Omicron XBB.1.5–neutralizing titers	HAI titers for seasonal influenza strains			
CCI BNT162b2 to BNT162b2		CCI BNT162b2 (Arm E)	BNT162b2 (Arm F)	Power[a]
CCI				
	CCI BNT162b2 to CCI	CCI BNT162b2 (Arm E)	CCI (Arm H)	Power[b]
	CCI			
	CCI BNT162b2 to QIV	CCI BNT162b2 (Arm E)	QIV (Arm G)	Power[b]
	CCI			
CCI				

9.5.2. Safety

For safety outcomes in the study, Table 8 shows the probability of observing at least 1 AE for a given true event rate of a particular AE with a sample size of 150, 300, 600, 1200, 1500, 3000, and 4500 participants.

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

Sample Size	Assumed True Rate of an AE	Probability of Having at Least 1 AE
150	0.01%	1.5%
150	0.05%	7.2%
150	0.1%	13.9%
300	0.01%	3.0%

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

Sample Size	Assumed True Rate of an AE	Probability of Having at Least 1 AE
300	0.05%	13.9%
300	0.1%	25.9%
600	0.01%	5.8%
600	0.05%	25.9%
600	0.1%	45.1%
1200	0.01%	11.3%
1200	0.05%	45.1%
1200	0.1%	69.9%
1500	0.01%	13.9%
1500	0.05%	52.8%
1500	0.1%	77.7%
3000	0.01%	25.9%
3000	0.05%	77.7%
3000	0.1%	95.0%
4500	0.01%	36.2%
4500	0.05%	89.5%
4500	0.1%	98.9%

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

10.1.3.1. Electronic Consent

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

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

The EDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the EDMC 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 endpoint events and of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

10.1.7. Data Quality Assurance

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

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

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

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

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and

requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

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

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

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

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

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

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

10.1.9. Use of Medical Records

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

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

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

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

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

10.1.10. Study and Site Start and Closure

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

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

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

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

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

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

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

10.1.11. Publication Policy

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

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

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

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

10.1.12. Sponsor's Medically Qualified Individual

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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

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

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

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

10.3.1. Definition of AE

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

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

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

10.3.2. Definition of an SAE

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

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

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

Assessment of Intensity

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/PSSA and in accordance with the SAE reporting requirements.

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

10.3.4. Reporting of SAEs

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

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either:

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

  OR

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

  Agree to use a male condom, and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.

  OR

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

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

  OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. 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.

3. Postmenopausal female:

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

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

Highly Effective Methods That Are User Dependent

6. Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated

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

Other Effective Methods

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

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

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

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, 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.
- 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 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.

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

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

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

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

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

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

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

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

10.7.2. Age-Specific Kidney Function Calculation Recommendations

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

eGFR (mL/min/1.73m²)

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

Female	if >0.7	if >0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤0.9	if ≤0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤0.9	if >0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if >0.9	if ≤0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if >0.9	if >0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

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10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 ms.
• Absolute value of QTcF >450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex >120 ms).
• New-onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

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

ECG Findings That Qualify as SAEs

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

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

10.9. Appendix 9: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

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

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

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

10.9.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in 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.

10.9.2. Definition of SAE, SADE, and USADE

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

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

10.9.3. Definition of Device Deficiency

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

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

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the unblinded site staff to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The unblinded site staff will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice. • If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF. • The unblinded site staff will notify the sponsor study team by contact method, eg, telephone, email, within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency. • The sponsor study team will capture the required information on the Medical Device Complaint form along with any associated AE (either serious or nonserious) when applicable and send to the appropriate product quality complaint group. • If the 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

Device Deficiency Recording
the role of the device in regard to the SAE must be included in the Vaccine SAE Report Form as outlined in Sections 8.4.1.1 and 8.4.1.2. • There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee. • For device deficiencies, it is very important that the 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.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

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

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

Known HIV infection

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

Known HCV infection

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

Known HBV infection

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

10.11. Appendix 11: Strain and Dose Selection

The selected modRNA vaccine dose level and strain to be used in this study will be based on Phase 1/2 safety and immunogenicity data and will be detailed in the IPM. The strains and doses that are selected can be found in Table 9.

Table 9. C5261001: qIRV/BNT162b2 and tIRV/BNT162b2 Combinations

Vaccine Group[a]	modRNA Vaccine	BNT162b2	CCI	Total modRNA Dose
3	CCI	30 µg		90 µg
11		30 µg		75 µg

a. The vaccine group is from C5261001, A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Combined Modified RNA Vaccine Candidates against COVID-19 and Influenza in Health Individuals, Substudy B.

10.12. Appendix 12: 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 1 (12 January 2024)

Overall Rationale for the Amendment: CCI [redacted]

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Increase in the total number of participants in Cohort 2 to 4500 by increasing the CCI /BNT162b2 (Omi XBB.1.5) study arm to 3000 participants and enrolling in a 2:1 ratio.	CCI [redacted] for a safety database of 3000 participants to support licensure of this combination.	1.1. Synopsis 4.1. Design 9.5.1. Immunogenicity
Nonsubstantial Modification(s)		
Description of situations where telehealth visits are permissible in the study.	To clarify that telehealth visits may be used for safety visits where blood draws are discontinued.	8.1.1. Telehealth Visits 8.10.3. Visit 2 8.10.4. Visit 3
CCI [redacted]		

Description of Change	Brief Rationale	Section # and Name
CCI [redacted]		
Further clarification of permissible corticosteroids by clarifying high- and low-dose and long- and short-term administration.	To provide additional clarity to the time frames and doses mentioned in PACL 2.0.	5.2. Exclusion Criteria 5.4. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention 6.9.1. Prohibited During the Study
Addition of ClinicalTrials.gov ID.	The ID became available after the initial protocol was written.	Title page 1.1. Synopsis
Clarified that all prior COVID-19 vaccination history and 3 years (prior to enrollment) of licensed or investigational influenza vaccine history was to be collected.	To provide a minimum requirement to sites on the collection of influenza vaccination history.	6.9. Prior and Concomitant Therapy
Minor editing of the rationale sections to focus on C5261001 Substudy B.	To ensure that the rationale sections are appropriate for this study.	1.1. Synopsis 2.1. Study Rationale
Minor clarifications of the cohort arms, including specifying the deltoid that was used for study intervention administration early in the study.	To further clarify which deltoid the vaccines are administered into.	4.1. Design

Description of Change	Brief Rationale	Section # and Name
Minor clarification of the interventions prohibited during the study resulting in exclusion from analysis of immunogenicity data, and minor typographical changes.	To provide additional clarity that medical interventions considered necessary should not be withheld, but they should result in exclusion from immunogenicity analysis.	6.9.1. Prohibited During the Study
Editing of text in AESI timelines to further clarify that AESIs, unless specified otherwise, should be collected after vaccination through 6 months. Section now consistent in description with other protocol sections.	To provide further clarity on the AESI collection timelines.	8.4.8. Protocol-Specified Adverse Events of Special Interest
Minor clarification that medication use indicated in the e-diary should be transcribed into the CRF.	To provide additional clarification of how medication use should be transcribed.	8.3.4.5. Antipyretic Medication
Update to the WHO antigen composition statement to indicate no change in strain composition recommendation.	To reflect the latest guidance in the WHO antigen composition statement for the COVID-19 vaccines.	2.2.3.1. SARS-CoV-2

Description of Change	Brief Rationale	Section # and Name
Description of preliminary data from Study C4781004.	To provide further evidence of influenza vaccine efficacy.	2.2.3.2. Influenza
Footnote added to Table 9 to indicate which study the vaccine groups are from.	To clarify that the vaccine groups in this table are related to a separate study.	10.11. Appendix 11: Strain and Dose Selection
Minor typographical changes throughout.	To correct minor typographical errors.	1.1. Synopsis 2.1. Study Rationale 2.2.3.1. SARS-CoV-2 2.2.3.3. Combined Influenza and COVID-19 Vaccines 3. Objectives, Endpoints, and Estimands 4.1. Design 6.1. Study Intervention(s) Administered 6.9.1. Prohibited During the Study 8.2. Immunogenicity Assessments 8.2.1. Testing for SARS-CoV-2 and Influenza Exposure 8.3.5. Pregnancy Testing 8.4.8. Protocol-Specified Adverse Events of Special Interest 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis 9.3.4. Exploratory Endpoint(s) 9.4.1. Analysis Timing

Description of Change	Brief Rationale	Section # and Name
PACL 2.0 (20 Dec 23): After enrollment of ~450 participants into Cohort 1, the IRT system will implement a pause on enrollment, allowing for observation of safety data following vaccination (including e-diary data, SAEs, AEs, and AESIs) for 60 days after vaccination. The EDMC will review the safety data prior to the continuation of enrollment of the remaining participants in Cohort 1.	CCI [redacted] modifications to further support the safety analysis of the combined CCI [redacted] and BNT162b2 (Omi XBB 1.5) vaccine (CCI [redacted] /BNT162b2 [Omi XBB.1.5]).	4.1. Design 6.3. Assignment to Study Intervention 9.5.2. Safety
PACL 2.0 (20 Dec 23): The time frames during which chronic systemic treatment with corticosteroids is prohibited during the study were updated to 60 days before and after enrollment for systemic corticosteroids at ≥20 mg/day prednisone or equivalent for ≥14 days, and	To clarify the different time frames within which chronic and short-term systemic corticosteroids are prohibited during the study.	6.9.1. Prohibited During the Study

Description of Change	Brief Rationale	Section # and Name
updated to 28 days before and after enrollment for systemic corticosteroids at ≥20 mg/day prednisone or equivalent for <14 days.		
PACL 1.0 (01 Dec 23): Addition that AEs are collected up to Visit 2, while SAEs are collected up to Visit 3.	To clarify the "active collection period" for collecting AE, SAE, and AESI information.	8.4.1. Time Period and Frequency for Collecting AE and SAE Information 1.2. Schema 2.3.1. Risk Assessment
PACL 1.0 (01 Dec 23): Update of the window for nonstudy vaccinations to 28 days before and 28 days after study vaccination.	To update the date where nonstudy vaccines are prohibited, to correct a typographical error.	6.9.1. Prohibited During the Study

10.13. Appendix 13: Abbreviations

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

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
AxMP	auxiliary medicinal product
CCI	[redacted]
β-hCG	beta-human chorionic gonadotropin
bIRV	bivalent influenza modRNA vaccine
BNT162b2	Pfizer-BioNTech COVID-19 vaccine
CBER	Center for Biologics Evaluation and Research (United States)
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations (United States)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
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
DCT	data collection tool
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate

Abbreviation	Term
eICD	electronic informed consent document
EMA	European Medicines Agency
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)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
CCI [redacted]	
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
CCI [redacted]	
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	Internet Protocol
IPAL	investigational product accountability log
IPM	investigational product manual
IRB	institutional review board
IRT	interactive response technology
IRV	influenza modRNA vaccine
ISO	International Organization for Standardization
IV	intravenous(ly)

Abbreviation	Term
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
Ln	natural log
LNP	lipid nanoparticle
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
NA	neuraminidase
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
NI	noninferiority
NIMP	noninvestigational medicinal product
Omi	Omicron
PACL	protocol administrative change letter
CCI	[redacted]
PCR	polymerase chain reaction
PFS	prefilled syringe(s)
PI	principal investigator
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QTcF	QT interval corrected by the Fridericia formula
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
S1	spike protein S1 subunit
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus

Abbreviation	Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Screat	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
ST-T	ST segment and T wave
SUSAR	suspected unexpected serious adverse reaction
T bili	total bilirubin
CCI	
Th1	T-helper type 1
tIRV	trivalent influenza modRNA vaccine
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States package insert
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

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Document Approval Record

Document Name:	C5261002 Clinical Protocol Amendment 2 Clean Copy, 11 Apr 2024
Document Title:	A PHASE 3, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A COMBINED MODIFIED RNA VACCINE CANDIDATE AGAINST COVID-19 AND INFLUENZA IN HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	11-Apr-2024 14:43:57	Business Line Approver
PPD	11-Apr-2024 15:07:26	Final Approval