A STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF COMBINED VACCINE CANDIDATE(S) AGAINST INFECTIOUS RESPIRATORY ILLNESSES, INCLUDING COVID-19 AND RSV, IN HEALTHY INDIVIDUALS

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Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title:

A Study to Learn About Combined Vaccine(s) Against Infectious Respiratory Illnesses, Including COVID-19 and RSV

Document History

Document	Version Date
Amendment 2	18 January 2024
Amendment 1	19 October 2023
Original protocol	22 April 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 (18 January 2024)

Overall Rationale for the Amendment:

Following a review of the needs of the overall development program, Substudy B was removed from the protocol.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Removed Substudy B	Following a review of the needs of the overall development program, Substudy B was removed from the protocol	Section 10.12 Appendix 12: Substudy B (Phase 1/2)
Nonsubstantial Modification(s)		
Removed text in the body of protocol that was specific to Substudy B	Following a review of the needs of the overall development program, Substudy B was removed from the protocol	Section 1.1 Synopsis Section 2.1 Study Rationale Section 2.2 Background Section 2.3 Benefit/Risk Assessment Section 4.2.2 Rationale for Comparator Section 4.3 Justification for Dose Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Description of Change	Brief Rationale	Section # and Name
		Section 8.4.8 Adverse Events of Special Interest
Removed references that were specific to Substudy B	Following a review of the needs of the overall development program, Substudy B was removed from the protocol	Sections 1 through 9 Section 10.1.5.1 Data Monitoring Committee Section 10.2 Appendix 2: Clinical Laboratory Tests Section 10.5 Appendix 5: Genetics

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1.1. Synopsis

Protocol Title:

A Study to Evaluate the Safety, Tolerability, and Immunogenicity of Combined Vaccine Candidate(s) Against Infectious Respiratory Illnesses, Including COVID-19 and RSV, in Healthy Individuals

Brief Title:

A Study to Learn About Combined Vaccine(s) Against Infectious Respiratory Illnesses, Including COVID-19 and RSV

Regulatory Agency Identification Number(s):

US IND Number:	29521
EU CT Number:	NA
ClinicalTrials.gov ID:	NCT05886777
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5481001
Phase:	1/2

Rationale:

Respiratory syncytial virus (RSV), influenza, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses are cocirculating infections, with a tendency to peak in winter. Vaccines against influenza and coronavirus disease 2019 (COVID-19) can be administered at a single healthcare visit as individual vaccinations, requiring multiple injections. The Pfizer RSV vaccine, RSV stabilized prefusion F subunit vaccine (RSVpreF), was recently found to be efficacious against RSV-associated lower respiratory tract illness (LRTI) in older adults (≥60 years of age). Concurrent administration of vaccines against these respiratory viral infections could reduce the need for multiple healthcare or pharmacy visits and may improve vaccine uptake. A combination vaccine with RSVpreF and Pfizer's COVID-19 vaccine (BNT162b2) would require 1 injection at a healthcare provider visit. A study of combined vaccination is required to investigate potential immunological interference in addition to safety and tolerability.

The nucleoside-modified messenger ribonucleic acid (modRNA) within BNT162b2 encodes the SARS-CoV-2 spike protein and is encapsulated in ribonucleic acid lipid nanoparticles (RNA-LNPs). BNT162b2 has demonstrated potent immunogenicity, high vaccine efficacy (VE), and a favorable safety profile in Phase 1, 2, and 3 human trials, as well as in real-world usage. At the time of study conduct, the relevant authorized/approved variant-adapted version of the BNT162b2 vaccine will be used in the substudy.

RSVpreF is a bivalent RSV prefusion F subunit vaccine developed by Pfizer. The RSV F glycoprotein facilitates fusion of the virion and host cell membrane through a dramatic transition from an unstable but highly immunogenic prefusion conformation to the more stable postfusion state. RSVpreF is composed of engineered, stabilized, trimeric, prefusion F glycoproteins matching the 2 subgroups (A and B) to help ensure the broadest coverage against RSV illness. RSVpreF efficacy against RSV-associated LRTI with ≥2 and ≥3 symptoms in older adults (≥60 years of age) was 66.7% and 85.7%, respectively. On 31 May 2023, the Food and Drug Administration (FDA) approved RSVpreF under the name Abrysvo™ for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age or older.

Given that annual vaccine programs against RSV and SARS-CoV-2 may be conducted in the future at a similar time of year, when influenza vaccine is also administered, developing combined vaccines targeting multiple viruses is likely to generate overall higher vaccination rates by allowing for more convenient scheduling than if these vaccinations were to be administered separately and/or at different visits. Hence, this study will include the following substudy:

- Substudy A: A Phase 1/2 substudy in up to approximately 1050 healthy participants ≥65 years of age to describe the safety, tolerability, and immunogenicity of a combined RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine [RSVpreF+BNT162b2], administered concomitantly with a seasonal influenza vaccine or administered alone.

Objectives, Endpoints, and Estimands

Please refer to the substudy appendix for the objectives and endpoints for the substudy.

Overall Design:

This is a master study to evaluate combined vaccine candidate(s) against infectious respiratory illnesses, including COVID-19 and RSV. The substudy design is detailed separately in the substudy appendix.

Substudy A (Phase 1/2)

This is a Phase 1/2 randomized, parallel-group, observer-blinded substudy to assess the safety, tolerability, and immunogenicity of a combined RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine [RSVpreF+BNT162b2], administered concomitantly with a seasonal influenza vaccine or administered alone. Approximately 1050 healthy participants ≥65 years of age will be enrolled in Substudy A.

Randomization will be conducted across 2 enrollment strata (see the table below).

Substudy A: Enrollment Strata

Enrollment Stratum	Total Number of Participants	Number of Participants per Vaccine Group	Vaccine Group Number	Vaccine Group Description
1	750	150	1	[RSVpreF+BNT162b2] administered concurrently in the opposite arm to licensed QIV
		150	2	[RSVpreF+BNT162b2] administered concurrently in the opposite arm to placebo
		150	3	Bivalent BNT162b2 administered concurrently in the opposite arm to placebo
		150	4	RSVpreF administered concurrently in the opposite arm to placebo
		150	5	Licensed QIV administered concurrently in the opposite arm to placebo
2	300	150	6	RSVpreF and bivalent BNT162b2 (2 injections in the same arm) coadministered concurrently in the opposite arm to placebo
		150	7	RSVpreF and bivalent BNT162b2 (2 injections in the same arm) coadministered concurrently in the opposite arm to licensed QIV

All participants will be asked to complete a reactogenicity electronic diary (e-diary) for 7 days following vaccination. Blood samples of approximately 50 mL will be collected for immunogenicity assessments prior to vaccination at Visit A101 and 1 month after vaccination (Visit A102).

E-diary data from Day 1 through Day 3 for the first 50 participants in Groups 1 to 5, and the first 20 participants in Groups 6 and 7, will be evaluated prior to enrollment of the remaining participants in each group.

Adverse events (AEs) will be collected from the signing of informed consent through Visit A102 (1-month follow-up visit). Serious adverse events (SAEs) will be collected from the signing of informed consent through Visit A103 (6-month telephone contact).

Substudy A will have stopping rules that will apply to groups receiving the combined RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine [RSVpreF+BNT162b2] as detailed in the protocol.

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

Number of Participants:

Substudy A (Phase 1/2)

Up to approximately 1050 participants will be enrolled in Substudy A (750 participants in enrollment stratum 1 and 300 participants in enrollment stratum 2).

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

Study Population:

Please refer to the substudy appendix for the inclusion and exclusion criteria of the substudy.

Study Arms and Duration:

Please refer to the appendix for the study arms and duration of the substudy.

Statistical Methods:

Statistical methods applicable to the substudy are specified in the body of the protocol. Statistical methods specific to the substudy are specified in the substudy appendix.

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.

1.2. Schema

Please refer to the study-specific appendix for the schema of the substudy.

1.3. Schedule of Activities

The schedule of activities (SoA) table(s) provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section (Section 8) 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(s), in order to conduct evaluations or assessments required to protect the well-being of the participant.

See Section 10.11.3 for the Substudy A SoA.

2. INTRODUCTION

2.1. Study Rationale

BNT162b2 (Comirnaty®) is an RNA-based vaccine that has been granted full marketing authorization, conditional marketing authorization, EUA, or temporary authorization in more than 100 countries for the prevention of COVID-19 caused by SARS-CoV-2.[1]

The modRNA within BNT162b2 encodes the SARS-CoV-2 spike protein and is encapsulated in RNA-LNPs. BNT162b2 has demonstrated potent immunogenicity, high VE, and a favorable safety profile in Phase 1, 2, and 3 human trials,[2] as well as in real-world usage.[3] As SARS-CoV-2 continues to circulate at very high levels,[4] Pfizer-BioNTech have developed a bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine, to further protect against COVID-19 caused by emergent and potentially more antigenically diverse variants. Bivalent BNT162b2 (original/Omi BA.4/BA.5), consisting of the original SARS-CoV-2 spike protein mRNA, targeting the ancestral strain of the virus, in combination with mRNA encoding the spike protein of the Omicron variant (BA.4/BA.5 sublineage), was therefore used in Substudy A.

RSVpreF is a bivalent RSV prefusion F subunit vaccine developed by Pfizer. The RSV F glycoprotein facilitates fusion of the virion and host cell membrane through a dramatic transition from an unstable but highly immunogenic prefusion conformation to the more stable postfusion state. RSVpreF is composed of engineered, stabilized, trimeric, prefusion F glycoproteins matching the 2 subgroups (A and B) to help ensure the broadest coverage against RSV illness. RSVpreF was recently found to be efficacious against RSV-associated LRTI in older adults,[5] and on 31 May 2023, the FDA approved RSVpreF under the name Abrysvo™ for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age or older.[6]

RSV and SARS-CoV-2 viruses often cocirculate, with a tendency to peak in winter.[7,8,9] In older adults, coadministration of vaccines in a single injection could reduce the need for multiple healthcare or pharmacy visits and improve vaccine uptake by reducing missed opportunities for a subsequent injection.[10] Studies of combination vaccination are required to investigate potential immunological interference in addition to safety and tolerability. Substudy A will investigate a combined RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine [RSVpreF+BNT162b2] administered concomitantly with a seasonal influenza vaccine or administered alone.

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.[11,12] Therefore, vaccines targeting the spike protein of SARS-CoV-2 have been used as a critical mitigation strategy of the COVID-19 pandemic. However, waning

effectiveness of the authorized vaccines has been shown to occur over time and is suspected to be due to waning of vaccine-induced immunity as well as the emergence of variants.

A large study conducted in 10 states within the US noted waning mRNA vaccine effectiveness against emergency room and urgent care encounters as well as hospitalizations, when comparing 2 months versus ≥4 months after receipt of a third dose. During the Omicron period, VE against emergency room or urgent care visits was 87% during the first 2 months after a third dose and decreased to 66% among those vaccinated 4 to 5 months earlier; VE against hospitalizations was 91% during the first 2 months following a third dose and decreased to 78% ≥4 months after a third dose.[13] In another large study conducted in approximately 2.5 million UK adults vaccinated with either ChAdOx1-S, BNT162b2, or mRNA-1273, approximately 80% of the participants with SARS-CoV-2 had Omicron variant infections and approximately 20% had Delta variant infections. In those who received 3 doses of BNT162b2, VE increased to 67.2% at 2 to 4 weeks before declining to 45.7% at 10 or more weeks.[14]

A 2021 laboratory study in Israel compared the neutralization of Omicron-infected cells in serum samples obtained from participants who had received 2 doses of BNT162b2 with neutralization in samples obtained from participants who had received 3 doses of BNT162b2. The neutralization efficiency of BNT162b2 was also tested against WT SARS-CoV-2 and the Beta, Delta, and Omicron variants. The importance of a third vaccine dose was evidenced by a higher neutralization efficiency (by a factor of 100) against the Omicron variant after the third dose compared to the second dose. However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant.[15]

The bivalent (original/Omi BA.4/BA.5) vaccine has shown improved neutralization of recent Omicron sublineages, which has translated to improved real-world protection against the Omicron variant.[16] Real-world studies show that bivalent mRNA vaccines increase protection relative to original monovalent-only mRNA vaccination against a range of COVID-19 outcomes, including symptomatic COVID-19 and severe illness, with higher effectiveness seen against more severe outcomes such as hospitalization.[17,18,19,20,21,22,23] Further, early evidence suggests that the bivalent vaccine may be more effective than the original monovalent mRNA booster in those 12 years of age or older during periods in which recent Omicron sublineages, including BA.5, BQ.1/BQ.1.1, and XBB.1 were prevalent.[16,21] At that time, Pfizer-BioNTech had developed a bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine to further protect against COVID-19 caused by emergent and potentially more antigenically diverse variants; this formulation was used in Substudy A.

But at present, Omicron and its sublineages continue to cause the majority of SARS-CoV-2 infections. The Omicron sublineage XBB.1.5 has been globally dominant since February 2023, while the prevalence of other XBB sublineages (ie, XBB.1.16, XBB.1.9.1, XBB.1.9.2, and XBB.2.3) is growing.[4] Sublineages XBB and XBB.1 are more antigenically distant from prior Omicron strain sublineages (eg, BA.2, BA.4/BA.5); more so than the distance of these early Omicron sublineages from the ancestral WT strain. They also show the greatest magnitude of immune escape that has been observed to date.[24,25,26] While the

bivalent BNT162b2 (original/Omi BA.4/BA.5)–adapted booster increased neutralizing titers against currently dominant strains, XBB.1.5 and XBB.1.16, the GMTs were substantially reduced compared to GMTs against the matched Omi BA.4/BA.5. Preclinical data showed an Omicron XBB–adapted vaccine (eg, Omicron XBB.1.5), when administered as a booster or 2-dose primary series, elicited higher neutralizing responses against Omicron XBB.1.5 and XBB.1.16 strains compared to the bivalent BNT162b2 (original/Omi BA.4/BA.5)–adapted vaccine. Based on these available data, FDA guidance, VRBPAC recommendation (held 15 June 2023),[27] and Pfizer/BioNTech strategies for manufacturing and testing using the same platforms, a variant-modified formulation targeting Omicron XBB.1.5 (approved 11 September 2023) for 2023/2024 became commercially available.[28]

2.2.2. RSV

RSV is a major cause of respiratory infection in all ages, which can result in severe illness in both infants and older adults. There are 2 antigenic variants of RSV: subgroups A (RSV A) and B (RSV B), which cocirculate.[29] Like influenza, RSV infection follows a seasonal pattern, causing yearly wintertime epidemics in temperate climates, usually between late autumn and early spring. In tropical climates, the outbreaks are generally associated with rainy seasons but are more unpredictable and frequently continuous.[30] Because of the COVID-19 pandemic, which spread worldwide in 2020-2021, the seasonality of several pathogens, including RSV, has been disrupted and the shift of peak incidence has been observed in a majority of geographic areas. RSV now cocirculates with influenza and SARS-CoV-2 and increases the incidence of respiratory infection–related disease.[7]

Adults ≥60 years of age are at increased risk of RSV infection, which can trigger exacerbations of underlying comorbid conditions such as COPD and CHF. RSV infection has been associated with up to 22% of acute COPD exacerbations in prospective cohort studies and 11% of wintertime hospitalizations for COPD exacerbations.[31] Current epidemiology shows that RSV is responsible for approximately 177,000 hospitalizations and 14,000 deaths annually in US adults 65 years of age and older.[32] Morbidity is significant among adults hospitalized with RSV disease, with 18% requiring intensive care, 31% needing home health services at discharge, and 26% dying within 1 year of hospitalization.[33] In the US, RSV disease incidence rates in older adults are approximately half those of influenza, with variation year to year.[34] Incidence rates and risk for severe complications from RSV infection are higher among immunocompromised adults and those with chronic conditions (eg, cardiopulmonary or renal disease, hematological malignancies, receipt of chemotherapy, or HIV infection).[35,36] However, the burden of adult RSV disease could be underestimated since testing for RSV is less common in older adults than in children.[37] RSV disease in adults is also difficult to diagnose based on clinical signs and symptoms alone, and, prior to the broader use of more sensitive detection methods, laboratory confirmation of RSV in adults was challenging because of low levels of virus shedding.[31]

RSV disease management in adults is limited to supportive measures, such as hydration and oxygenation. Aerosolized ribavirin has limited evidence of effectiveness and is predominantly restricted to severely immunocompromised hospitalized patients because of inconvenient administration, teratogenicity, anemia concerns, and high cost.[38] As of 31 May 2023, Abrysvo has been approved for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older by the FDA.[6] Abrysvo has also been approved for the prevention of lower respiratory tract disease caused by RSV in pregnant individuals 32 through 36 weeks gestational age by the FDA.[39]

2.2.3. Clinical Overview

2.2.3.1. SARS-CoV-2

Study C4591001 (NCT04368728) is an ongoing Phase 1/2/3 trial in ~46,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from a novel RNA-based vaccine candidate.[40] The trial is being conducted in a heterogeneous study population: eligible participants ≥12 years of age; healthy participants, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants. The study consists of 2 parts: Phase 1: to identify the preferred vaccine candidate (BNT162b1 or BNT162b2) and dose level (10 µg, 20 µg, 30 µg, or 100 µg [for BNT162b1]); Phase 2/3: an expanded-cohort and efficacy part to evaluate the selected vaccine candidate (BNT162b2).

The 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. BNT162b2 was selected from the Phase 1 part of the study based on the overall safety, tolerability, and immunogenicity. 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. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, sexes, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.[41]

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.[42] 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 included 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.[41]

A booster dose (Dose 3) of BNT162b2 was administered to 306 Phase 3 participants without prior evidence of SARS-CoV-2 infection ~6 months after completing the 2-dose schedule. The immune response 1 month after administration of Dose 3 was noninferior to that observed 1 month after Dose 2 in the same participants. Furthermore, from the same analysis, among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 3, a high proportion of participants (99.5%) had a seroresponse at 1 month after Dose 3 compared with 98.0% at 1 month after Dose 2.[2]

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.[43] 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.[44] 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.

The per-protocol interim safety and efficacy analysis was conducted in October 2021 for Study C4591031 Substudy A. In this study, approximately 10,000 participants who had previously received 2 doses of BNT162b2 as a primary series in Study C4591001 were randomized 1:1 in Study C4591031 to receive either a 30-µg booster dose (the same dosage strength as in the 2-dose primary series) or placebo. The time between the second dose and administration of the booster dose or placebo for most participants was ≥10 to <12 months.

Symptomatic COVID-19 occurrence was measured from ≥7 days after booster or placebo, with a median follow-up of 2.5 months. During the blinded placebo-controlled study period up to a data cutoff date of 05 October 2021, there were a total of 6 cases of COVID-19 in the booster group and 123 cases in the nonboosted placebo group, in the evaluable efficacy population without evidence of prior SARS-CoV-2 infection. The observed relative VE was 95.3% (2-sided 95% CI: 89.5%, 98.3%), which reflects the reduction in disease occurrence in the boosted group versus the nonboosted group. The AE profile was generally consistent with other previously submitted clinical safety data for the vaccine, with no new safety concerns identified. No cases of myocarditis or pericarditis were reported.[45]

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, 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 AE profile for Omicron BA.1–modified BNT162b2 vaccines. In participants >18 through 55 years of age, the bivalent Omicron-modified vaccine at the 30-µg dose level showed a similar local reaction and systemic event reactogenicity profile as the prototype BNT162b2 vaccine. 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 vaccine-elicited immune response to the bivalent Omicron BA.1–modified vaccines when administered as a booster (Dose 4) to BNT162b2-experienced participants 18 through 55 years of age. Bivalent Omicron-modified vaccines (BNT162b2 + BNT162b2 Omi 30 µg and 60 µg) met the defined superiority criteria against Omicron BA.1 and noninferiority response to the reference strain, in participants within the group >55 years of age. Based on the 1-month postdose safety and immunogenicity findings from the C4591031 Substudy E >55-year age group, the FDA granted EUA on 31 August 2022 for the bivalent vaccine as a single booster dose for individuals 12 years of age and older.[46]

The SARS-CoV-2 Omicron variant B.1.1.529 emerged in late 2021 and quickly became the dominant circulating strain worldwide, replacing earlier strains and variants. In the US, the Omicron BA.1 sublineage was replaced by the BA.2 sublineage in April 2022 and subsequently was replaced by BA.4 and BA.5 sublineages by July 2022.[47] The BA.4 and BA.5 sublineages demonstrate substantial immune escape from neutralizing antibodies induced by both infection and immunization,[48] which has been attributed to the L452R and F486V spike mutations within the protein sequence of BA.4 and BA.5.[49] Moreover, studies have demonstrated that the effectiveness of BNT162b2 against SARS-CoV-2 infection and COVID-19 wanes over a period of months, particularly in the context of variants.[13,14,50] In light of the waning effectiveness of the 2-dose primary series of BNT162b2 as well as the existence of variants with cumulative mutations in the spike protein that are resilient to the

existing immune response, particularly Omicron, an enhanced bivalent vaccine was developed. Study C4591044 is currently evaluating bivalent BNT162b2 (original/Omi BA.4/BA.5) consisting of the LNP-formulated original SARS-CoV-2 spike protein mRNA, targeting the ancestral strain of the virus, in combination with LNP-formulated mRNA encoding the spike protein of the Omicron variant (BA.4/BA.5 sublineage) in approximately 900 participants ≥12 years of age. Preliminary data from this study demonstrate a robust neutralizing immune response 1 month after a 30-µg booster dose of Omicron BA.4/BA.5–adapted bivalent COVID-19 vaccine (Pfizer-BioNTech COVID-19 vaccine, bivalent [original and Omicron BA.4/BA.5]). Immune responses against the BA.4/BA.5 sublineages were substantially higher for those who received the bivalent vaccine compared to the companies' original COVID-19 vaccine, with a similar safety and tolerability profile between both vaccines.[51]

Omicron BA.4/BA.5 remained dominant in the US until October 2022, when they were replaced by XBB and BQ.1 sublineages. BQ.1 is a subvariant of BA.5, but XBB is a recombinant subvariant, combining BA.2.10.1 and BA.2.75.[52] Preliminary data comparing immune responses to the monovalent BNT162b2 (original) vaccine and the bivalent BNT162b2 (original/Omi BA.4/BA.5) in adults >55 years of age who had received 3 prior doses of monovalent BNT162b2 showed that bivalent BNT162b2 (original/Omi BA.4/BA.5) induced higher GMFRs against BA.4/BA.5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1, suggesting that the bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine is more immunogenic against circulating Omicron sublineages compared with the original BNT162b2 monovalent vaccine.[53]

Data on SARS-CoV-2 evolution indicated that Omicron XBB sublineages accounted for more than 95% of the circulating virus variants in the US as of early June 2023. While XBB.1.5 has declined to less than 40% of presumed circulating virus in the US, XBB.1.16 is on the rise and XBB.2.3 is slowly increasing in proportion. The current trajectory of virus evolution suggests that XBB.1.16 could be dominant by fall 2023. XBB.2.3 and other XBB sublineages could also continue to increase in proportion as the virus evolves. Although SARS-CoV-2 continues to evolve, the protein sequences of the XBB.1.5, XBB.1.16, and XBB.2.3 spike proteins appear similar, with few amino acid differences. Available evidence suggests little to no further immune evasion from these new substitutions in the XBB.1.16 spike protein compared to XBB.1.5. By several measures, including escape from antibody neutralization and waning protection, the bivalent COVID-19 (original/Omi BA.4/BA.5) vaccines appear less effective against currently circulating variants (eg, XBB-lineage viruses) than against previous strains of virus. The totality of available evidence suggested that a monovalent XBB-lineage vaccine was warranted for the 2023-2024 update, and the FDA has advised that manufacturers seeking to update their COVID-19 vaccines should develop vaccines with a monovalent XBB.1.5 composition, which was approved on 11 September 2023 in US.[28,54]

2.2.3.2. RSVpreF Vaccination

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

RSVpreF is being developed for 2 indications:

- **Older Adult:** Prevention of ARI-RSV and LRTI-RSV in adults 60 years of age and older via active immunization.

- **Maternal:** Prevention of LRTI-RSV and severe LRTI-RSV in infants by active immunization of pregnant women.

As of September 2023, RSVpreF has been studied in healthy adults and pregnant women. RSVpreF was shown to be well tolerated, with an acceptable safety profile, and highly efficacious in older adults and infants of women vaccinated during pregnancy.

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

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

- Phase 1/2 study C3671002, in 313 older adults 65 through 85 years of age, studied the 3 dose levels of RSVpreF with $Al(OH)_3$, or $CpG/Al(OH)_3$ (60 µg, 120 µg, and 240 µg), given as a single dose or on a schedule of 2 doses administered 2 months apart. All RSVpreF doses and formulations elicited high RSV A– and RSV B–neutralizing

antibody GMTs 1 month after vaccination (GMFRs ranging from 4.8 to 11.6 and 4.5 to 14.1, respectively). CpG-containing formulations did not further increase neutralizing GMTs compared to RSVpreF with or without $Al(OH)_3$. GMTs in all groups declined but remained higher than baseline (before vaccination) and placebo (SIIV only) at 12 months after vaccination (GMFRs ranging from 2.1 to 3.5 and 2.2 to 4.3, respectively). No increase in GMTs was observed 1 month after Vaccination 2 (GMFR of 0.9). All doses and formulations were safe and well tolerated.

- Study C3671014 is a completed Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind lot-consistency study in a population of up to 1000 healthy adults 18 to ≤49 years of age. The study examined the immune response and the safety and tolerability profiles across 3 manufactured lots of RSVpreF when administered as a single 120-µg dose to healthy adults. The primary analyses showed that the ratios of neutralizing GMTs for each of the 3 manufactured RSVpreF lots 1 month after vaccination are equivalent, and that the 120-µg dose of RSVpreF is well tolerated and has an acceptable safety profile.

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

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

- C3671006 is a completed Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study designed to assess the safety and immunogenicity of RSVpreF when coadministered with SIIV compared to sequential administration of the vaccines when given 1 month apart (SIIV followed by RSVpreF). Approximately 1400 healthy adults ≥65 years of age were randomized 1:1 to either a coadministration group or a sequential-administration group. The intention was to demonstrate that the immune responses generated with a 120-µg RSVpreF dose coadministered with SIIV were noninferior to the immune responses when these products were administered 4 weeks apart. The safety and tolerability of RSVpreF were also examined. Results demonstrated noninferiority of the RSVpreF and SIIV immune responses when RSVpreF was coadministered with SIIV. The results of this study support the acceptability of coadministration of RSVpreF and SIIV in an older adult population.

- C3671016 is Phase 1/2/3 study in participants 2 to <18 years of age at high risk of RSV disease initiated in June 2023.[55] The study consists of 2 phases: Phase 1 and Phase 2/3. Phase 1 is an open-label, age descending, dose-finding study and Phase 2/3 is a placebo-controlled, randomized, double-blinded study to evaluate the safety, tolerability, and immunogenicity of RSVpreF. Both the 120-µg dose level and a 60-µg dose level will be evaluated. Approximately 120 participants will be enrolled in the Phase 1 cohort and up to 1860 participants will be enrolled in the Phase 2/3 cohort.

- C3671023 is a Phase 3 study to evaluate the safety, tolerability, and immunogenicity of RSVpreF in adults at high risk of severe RSV disease. The study is divided into 2 substudies: Substudy A and Substudy B. Substudy A is a double-blinded, randomized, placebo-controlled trial, enrolling participants ≥18 to <60 years of age who are at high risk for severe RSV disease due to underlying medical conditions, such as COPD, asthma, and CHF, or due to living in a skilled-nursing facility. Participants (N=675) will be randomized 2:1 to 1 dose of RSVpreF or placebo and followed for 6 months. Substudy B is an open-label trial which has completed enrollment of participants age 18 years and older with immunocompromising conditions. Participants (approximately N=200) received 2 doses (1 month apart) of RSVpreF and were followed for 6 months after the last dose.

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

2.3. Benefit/Risk Assessment

The available safety, immunogenicity, and effectiveness data from ongoing clinical trials for RSVpreF and BNT162b2 support a favorable benefit/risk profile and support clinical development of a vaccine combining these components. The stability of RSVpreF and LNP mRNA formulation has been assessed, and there is no observed difference in stability profile of RSVpreF as a result of mixing with LNP.

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 RSV and SARS-CoV-2 that would align with the recent FDA recommendations for an annual COVID-19 vaccination approach.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of bivalent BNT162b2 (original/Omi BA.4/BA.5) and RSVpreF may be found in their IBs, which are the SRSDs for this study. The SRSD for QIV is the Fluzone HD USPI. Refer to the Study Intervention(s) table in Section 6 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): [RSVpreF+BNT162b2]		
The potential risks for the combination vaccine are expected to be similar to the potential risks for the individual components as detailed below.	It is anticipated that common adverse reactions seen with the individual components will also be seen with the combination vaccine, as detailed below.	The mitigations for the combination vaccine will be similar to the mitigations for the individual components as detailed below.
Study Intervention(s): BNT162b2, BNT162b2 Omicron (BA.4/BA.5 Sublineage)		
For BNT162b2 Omicron (BA.4/BA.5 sublineage): These vaccines have the same modRNA platform (with sequence changes limited to those that are Omicron specific) and LNP formulation as BNT162b2; therefore, the safety profile is expected to be similar to that of BNT162b2, ie, local reactions, such as injection site redness, injection site swelling, and	These are common adverse reactions seen with other vaccines as well as the COVID-19 vaccine. Data available from the C4591001 study (with BNT162b2) showed low incidence of severe or serious events and no clinically concerning safety observations across the safety	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
injection site pain, and systemic events, such as fever, fatigue, headache, chills, 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.	population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status.[41] Anaphylaxis: Frequency not known. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. 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 cases are generally mild, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients. Postauthorization safety data surveillance has confirmed the safety profile observed in Study C4591001 and has resulted in identification of some additional adverse reactions (risks) as noted in the SRSD.	AEs will be collected from the signing of informed consent through Visit 2 (1-month follow-up visit). SAEs will be collected from the signing of informed consent through Visit 3 (6-month telephone contact). Specific references to risks and events of interest are made within the ICD, with reporting instructions if a case is suspected.
Study Intervention(s): RSVpreF		
For **RSVpreF**: Pfizer has identified the most common risks for RSVpreF as local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fatigue, headache, diarrhea, joint pain, nausea, vomiting, muscle pain, and fever.[39]	These are common adverse reactions seen with other vaccines as well as RSVpreF.[57] Data available from completed and ongoing studies showed a low incidence of severe or serious events, and no clinically	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Guillain-Barré syndrome has been identified as a potential risk for RSVpreF. Other events of interest include atrial fibrillation, polyneuropathy, preterm birth (delivery at <37 0/7 weeks' gestation), and hypertensive disorders of pregnancy.[56] The identified adverse reactions in local product labels may vary depending on the requirements of the respective regulatory authorities (eg, EU SmPC and USPI).	concerning events. The vaccine appears to be safe and well tolerated across the safety population and within demographic subgroups based on age, sex, and race/ethnicity.[58] In Study C3671013, conducted in adults 60 years of age and older, there was 1 case of Guillain-Barré syndrome and 1 case of Miller Fisher syndrome (both with a plausible temporal relationship with vaccination). Both cases had confounding factors or an alternative etiology. In Study C3671013, conducted in adults 60 years of age and older, there was a nonsignificant numerical imbalance in the number of cases of atrial fibrillation reported for individuals who received RSVpreF compared to individuals who received the placebo. Most of the participants who had atrial fibrillation and received RSVpreF had a preexisting medical history of atrial fibrillation and/or cardiac disease.[59]	All study participants will be observed for at least 30 minutes after vaccination. AEs will be collected from the signing of informed consent through Visit 2 (1-month follow-up visit). SAEs will be collected from the signing of informed consent through Visit 3 (6-month telephone contact). Specific references to risks and events of interest are made within the ICD, with reporting instructions if a case is suspected.
Study Intervention(s): QIV		
Local and systemic reactions to the vaccine may occur.	The following summary represents an example QIV safety profile. In adults 65 years of age and older, the most commonly reported injection-site adverse reaction was pain (41.3%). The most commonly reported systemic adverse reactions were myalgia (22.7%),	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	headache (14.4%), and malaise (13.2%).[60]	All study participants will be observed for at least 30 minutes after vaccination. AEs will be collected from signing of the ICD through 1 month and SAEs through 6 months after study vaccination.
Study Procedures		
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants enrolled in Substudy A are detailed in Section 10.11.4.3.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with RSVpreF and BNT162b2 RNA-based COVID-19 vaccines are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

See Section 10.11.5 for the Substudy A objectives, endpoints, and estimands.

4. STUDY DESIGN

4.1. Overall Design

See Section 10.11.6 for the Substudy A design.

4.2. Scientific Rationale for Study Design

See Section 2.1.

See the substudy appendix for the rationale supporting the substudy.

4.2.1. Diversity of Study Population

The team will follow best practices for diverse study population enrollment and retention, which will include engaging with sites that have historically been shown to recruit diverse participants and/or are geographically located in diverse communities. Early and ongoing site interactions will include diversity discussions, and diversity materials will be provided to support the sites' participant engagements.

4.2.2. Rationale for Comparator

Active comparators to the combination vaccine [RSVpreF+BNT162b2] have been chosen for Substudy A, including individual injections of RSVpreF and bivalent BNT162b2. The doses for these comparators were chosen based on the doses that demonstrated efficacy in the pivotal Phase 3 study (RSVpreF) and the dose granted with an EUA by the FDA (bivalent BNT162b2 [original/Omi BA.4/BA.5]).

4.2.3. Choice of Contraception/Barrier Requirements

Abrysvo (for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years and older) has not been studied in pregnant individuals less than 24 weeks gestational age and in those at increased risk for preterm birth, and available data on Comirnaty (for the prevention of COVID-19 caused by SARS-CoV-2) administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. The use of a highly effective method of contraception is required for sexual intercourse involving a WOCBP (see Section 10.4.3).

4.3. Justification for Dose

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

The FDA has granted EUA for the use of bivalent BNT162b2 (original/Omi BA.4/BA.5) at a dose level of 30 µg (15 µg original BNT162b2 and 15 µg BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5]) in individuals ≥12 years of age,[61] and this dose level is being used when bivalent BNT162b2 (original/Omi BA.4/BA.5) is administered alone and as part of the RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine [RSVpreF+BNT162b2] administered in Substudy A.

4.3.2. RSVpreF

The 120-µg dose, without any adjuvants, was the dose that demonstrated efficacy in the pivotal Phase 3 study in adults 60 years of age and older. This dose has been shown to be well tolerated. This dose also demonstrated no interference when administered concurrently with a seasonal influenza vaccine (Study C3671006).[5]

The dose and formulation for Substudy A is 120 µg RSVpreF without any adjuvants.

4.3.3. Combined RSVpreF and Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Vaccine [RSVpreF+BNT162b2]

The dose and formulation for Substudy A is based on the combination of the individual components of the vaccine as detailed in Section 10.11.8.

4.4. End of Study Definition

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

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

The end of the overall study is the last visit of the last participant in the substudy to be completed.

5. STUDY POPULATION

The substudy can fulfill the 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 substudy is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

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

5.1. Inclusion Criteria

See Section 10.11.7.1 for the Substudy A inclusion criteria.

5.2. Exclusion Criteria

See Section 10.11.7.2 for the Substudy A exclusion criteria.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Section 10.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

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

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

5.4. Screen Failures

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

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

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

See Section 10.11.7.3 for temporary delay criteria for Substudy A.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

See Section 10.11.8 for study intervention(s) and concomitant therapy for Substudy A.

6.1. Study Intervention(s) Administered

See Section 10.11.8.1 for study interventions to be administered during Substudy A.

6.1.1. Administration

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

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

Study intervention administration details will be recorded on the CRF.

See Section 10.11.8.1.1 (Substudy A) for study intervention administration details.

6.1.2. Medical Devices

In this study, medical devices being deployed are for the reconstitution diluent for some of the study interventions.

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

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

the excursion definition and information to report for each excursion will be provided to the site in the IPM.

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

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

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

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

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

6.2.1. Preparation and Dispensing

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

See Section 10.11.8.1.3.1 for further details regarding preparation and dispensing for Substudy A.

6.3. Assignment to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including, but not limited to, the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number*. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. This report will be provided to blinded or unblinded site staff as appropriate on the role/permission the user is granted and must be stored in the site's blinded or unblinded files as appropriate.

* 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(s).

6.4. Blinding

See Section 10.11.8.2 for Substudy A blinding arrangements.

6.4.1. Blinding of Participants

Substudy A blinding arrangements for participants are detailed in Section 10.11.8.2.1.

6.4.2. Blinding of Site Personnel

Substudy A blinding arrangements for site personnel are detailed in Section 10.11.8.2.2.

6.4.3. Blinding of the Sponsor

Substudy A blinding arrangements for the sponsor are detailed in Section 10.11.8.2.3.

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

Dose modification is NA to this protocol.

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

6.8. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

6.9. Prior and Concomitant Therapy

See Section 10.11.8.7 for Substudy A prior and concomitant therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is NA.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures
- Lost to follow-up
- Death
- Study terminated by sponsor

- AEs
- Participant request
- Investigator request

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.

When a participant is withdrawn from the study, the investigator will complete the 6-month telephone contact if the participant has received study intervention.

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(s). Protocol waivers or exemptions are not allowed.

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

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

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

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

8.1.1. Telehealth Visits

If in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants.

In the event that a clinic visit cannot be conducted, telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring.

The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 10.3.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 10.4.
- Study participants must be reminded to promptly notify site staff about any change in their health status.

Additionally, for Substudy A:

- Obtain stop dates for previously reported AEs and SAEs.
- Obtain stop dates for any reactogenicity events reported as present on the last day of e-diary completion.
- Record the use of **prohibited** medications in the CRF as noted in Section 10.11.8.7.1.
- Record the use of any new nonstudy vaccines in the CRF.

8.2. Efficacy and/or Immunogenicity Assessments

See Section 10.11.10.1 for Substudy A immunogenicity assessments.

8.2.1. Biological Samples

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

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

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

8.3. Safety Assessments

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

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

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

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

Safety parameters also include reactogenicity e-diary reports of local reactions, systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.3.4.

8.3.1. Physical Examinations

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Section 10.3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

For details, refer to the substudy appendix.

8.3.2. Vital Signs

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Section 10.3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

For details, refer to the substudy appendix.

8.3.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study. Measurement of troponin will be performed locally for potential myocarditis/pericarditis evaluation.

For details, refer to the substudy appendix.

8.3.4. Electronic Diary

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

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

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

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

8.3.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[57]

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. In Substudy A, local reactions will be assessed at the injection site on the right arm.

If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

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

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person 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 1. 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 2.

If a systemic event persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

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 and, if it is determined

to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	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 in the evening daily during the reactogenicity e-diary reporting period. 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 3 during analysis.

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

Table 3. 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 reporting period (Day 1 through Day 7).

8.3.5. Stopping Rules

Stopping rules will be employed in Substudy A; see Section 10.11.10.5.

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

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Sections 10.10.1 and 10.10.2. Device deficiencies are covered in Section 10.10.3.

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 A102 (1-month follow-up visit), per the SoA in the substudy appendix.

Record any AEs that occur within the 48 hours after the blood draw.

SAEs will be collected from the time the participant provides informed consent through and including Visit A103 (6-month follow-up visit), per the SoA in the substudy appendix.

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the study intervention.

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

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

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female 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 Reporting Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Deaths 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 considered AESIs:

- Confirmed diagnosis of influenza.
- Confirmed diagnosis of RSV infection.
- Confirmed diagnosis of myocarditis or pericarditis occurring within 4 weeks after vaccination. See Section 10.11.10.7.5.
- Confirmed COVID-19 diagnosis (clinical signs/symptoms per the CDC[62] and positive SARS-CoV-2 NAAT or rapid antigen test result).
- Diagnosis of Guillain-Barré syndrome.
- Diagnosis of acute polyneuropathy without an underlying etiology.
- Diagnosis of atrial fibrillation.
- Preterm delivery (delivery at <37 0/7 weeks' gestation).
- Diagnosis of a hypertensive disorder of pregnancy.

- Details of the AESIs listed above are further defined in the investigator site file.

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

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.3. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Reporting Form.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

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

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

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.4.1 through 8.4.3 and Section 10.3.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

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

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

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

The method of documenting medical device deficiencies is provided in Section 10.10.

8.4.9.2. Follow-Up of Medical Device Deficiencies

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

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

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

8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The unblinded site staff notifies the sponsor by a contact method as detailed in the IPM within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

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

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

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

The sponsor will be the contact for the receipt of device deficiency information.

8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies

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

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

8.4.10. Vaccination Errors

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

Vaccination errors are recorded and reported as follows:

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

Vaccination errors include:

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

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

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

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

NA for Substudy A.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

See Section 10.11.10.1 for Substudy A.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

Refer to Section 10.11.11.1 for statistical hypotheses for Substudy A.

9.2. Analysis Sets

Refer to Section 10.11.11.2 for analysis sets in Substudy A.

9.3. Statistical Analyses

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

Statistical analyses for Substudy A are detailed in Section 10.11.11.3.

9.3.1. General Considerations

Unless stated otherwise, “vaccine group” in this section refers to the study intervention group. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. In general, completely missing reactogenicity e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For partially complete e-diary data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on missing days based on the e-diary data source. Missing AE dates will be handled according to the Pfizer safety rules.

The estimands to evaluate the immunogenicity objective are based on the evaluable immunogenicity population. These estimands estimate the immune response after study intervention in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be

performed based on the mITT immunogenicity population if there is a large enough difference in sample size between the mITT immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing immunogenicity results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

9.3.1.1. Analyses for Binary Data

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

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

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

9.3.1.2. Analyses for Continuous Data

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

CIs for the mean of the continuous variables will be constructed by the standard method based on the Student t distribution.

9.3.1.2.1. Geometric Mean

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

9.3.1.2.2. Geometric Mean Fold Rises

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

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

9.3.1.2.3. Geometric Mean Ratios

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

9.3.1.2.4. Reverse Cumulative Distribution Curves

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

9.4. Interim Analyses

Details for interim analyses will be provided in Section 10.11.11.4 for Substudy A.

9.5. Sample Size Determination

Refer to Section 10.11.11.5 for sample size determination related to Substudy A.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

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

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

The responsibilities of the IRC will include at a minimum:

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

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 data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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

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

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

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

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

10.1.8. Source Documents

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

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

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

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

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

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

10.1.9. Use of Medical Records

Not applicable.

10.1.10. Study and Site Start and Closure

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

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

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

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

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

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

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

10.1.11. Publication Policy

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

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

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

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

10.1.12. Sponsor's Medically Qualified Individual

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

Routine clinical laboratory tests are NA to Substudy A.

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

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

suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

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

10.3.4. Reporting of SAEs

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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 in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

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

10.4.4. Contraception Methods

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

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 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

NA for Substudy A.

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

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

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate eGFR (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 (for adult and for pediatric participants). Screat and reflex Scys values are needed to estimate the combined Screat-Scys eGFR calculation to ascertain whether eGFR change from baseline is comparable for 2021 CKD-EPI eGFR Screat-only and for 2021 CKD-EPI eGFR combined Screat plus Scys (for adult participants only).

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

10.7.2. Age-Specific Kidney Function Calculation Recommendations

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

eGFR (mL/min/1.73m²)

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

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

10.7.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at screening, baseline, and postbaseline visits. Site calculations of kidney function can be performed manually, using the age-appropriate formulae (see Section 10.7.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The US National Kidney Foundation Online Calculators:

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator
- Adolescents (12 years to <18 years) - Cockcroft-Gault Formula (eCrCl): https://www.kidney.org/professionals/kdoqi/gfr_calculatorCoc

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

10.7.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

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

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30-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: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

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

Known HIV infection

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

Known HCV infection

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

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation

10.10. Appendix 10: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

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

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

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

10.10.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (Section 10.3.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.10.2. Definition of SAE, SADE, and USADE

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

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

10.10.3. Definition of Device Deficiency

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

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

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the unblinded site staff to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The unblinded site staff will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and will also capture the required information on the Medical Device Complaint form. • It is **not** acceptable for the unblinded site staff to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form. • There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. • If the unblinded site staff determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the unblinded site staff will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as

the AE or SAE rather than the individual signs/symptoms. Requirements for recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.3).

- For device deficiencies, it is very important that the unblinded site staff describe any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

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

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency

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

10.10.5. Reporting of SAEs

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

10.10.6. Reporting of SADEs

SADE Reporting to Pfizer Safety

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

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.11. Appendix 11: Substudy A (Phase 1/2)

10.11.1. Synopsis – Substudy A

See Section 1.1.

10.11.2. Schema – Substudy A (Phase 1/2)

	Vaccination			1-Month Follow-Up Visit	6-Month Telephone Contact
Approximate Month (Visit Window)	**0 (Day 1)**			**1 (28 to 35 Days After Vaccination)**	**6 (175 to 189 Days After Vaccination)**
Visit Identifier	**Visit A101**			**Visit A102**	**Visit A103**
	Vaccination 1 (Right Arm)	**Vaccination 2 (Left Arm)**	**Vaccination 3 (Right Arm)**		
Group 1 (n=150)	Combination [RSVpreF+BNT162b2]	QIV			
Group 2 (n=150)	Combination [RSVpreF+BNT162b2]	Placebo			
Group 3 (n=150)	Bivalent BNT162b2	Placebo			
Group 4 (n=150)	RSVpreF	Placebo			
Group 5 (n=150)	QIV	Placebo			
Group 6[a] (n=150)	Bivalent BNT162b2	Placebo	RSVpreF		
Group 7[a] (n=150)	Bivalent BNT162b2	QIV	RSVpreF		

a. Separate administration sites on right arm by 1 inch (2.5 cm).

10.11.3. SoA – Substudy A (Phase 1/2)

Visit Identifier	A101	A102	A103	Notes
Visit Description	**Vaccination**	**1-Month Follow-Up Visit**	**6-Month Telephone Contact**	
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit A101**	**175 to 189 Days After Visit A101**	**Day 1 = Day of Vaccination**
Obtain informed consent	X			See Section 10.1.3.
Assign participant number	X			See Section 6.3.
Obtain demography and medical history data* (including confirmed COVID-19 diagnosis or asymptomatic positive SARS-CoV-2 test result [NAAT or antigen test])	X			* Include date of onset and resolution (if applicable).
Perform clinical assessment	X			Including, if indicated, a physical examination. Examinations and assessments must occur prior to vaccination. See Section 8.3.1.
Measure height and weight	X			
Measure vital signs (including oral temperature)	X			Blood pressure and pulse rate; see Section 8.3.2.
Confirm use of contraceptives (if appropriate)	X	X		See Section 10.4.3
Collect prior COVID-19 vaccine information	X			
Collect details of any influenza vaccine received in the prior 12 months	X			Include product name and date of administration.
Collect nonstudy vaccine information	X	X	X	See Section 10.11.8.7.
Collect prohibited medication use		X	X	See Section 10.11.8.7.1.
Confirm eligibility	X			See Section 10.11.7. Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
Obtain randomization number and study intervention allocation	X			Do not randomize until eligibility is confirmed and the participant is present. See Section 6.3.
Collect blood sample for immunogenicity assessment	~50 mL†	~50 mL		† Prior to vaccination.

Visit Identifier	A101	A102	A103	Notes
Visit Description	**Vaccination**	**1-Month Follow-Up Visit**	**6-Month Telephone Contact**	
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit A101**	**175 to 189 Days After Visit A101**	**Day 1 = Day of Vaccination**
Administer study intervention	X			See Section 10.11.8.1.1.
Assess acute reactions for at least 30 minutes after study intervention administration	X			Must include time of onset.
Explain to the participant e-diary completion requirements and assist the participant with downloading the application or issue provisioned device if required	X			See Section 8.3.4.
Provide thermometer and measuring device	X			
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	X			Days 1 through 7.
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		See Section 8.3.4.
Collect AEs and SAEs as appropriate	X	X	X	
Collect e-diary or assist the participant with deleting application		X		Ensure all e-diary data have been transferred prior to e-diary deactivation or removal of the app.

10.11.4. Introduction – Substudy A

10.11.4.1. Substudy A Rationale

This is a Phase 1/2 substudy in up to approximately 1050 healthy participants ≥65 years of age to describe the safety, tolerability, and immunogenicity of a combined RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine [RSVpreF+BNT162b2], administered concomitantly with a seasonal influenza vaccine or administered alone.

10.11.4.2. Background

See Section 2.2.

10.11.4.3. Benefit/Risk Assessment

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

Benefits to individual participants enrolled in Substudy A may be:

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

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

10.11.5. Objectives, Endpoints, and Estimands – Substudy A

Substudy A (Phase 1/2)		
Objectives	**Estimands**	**Endpoints**
Primary	**Primary**	**Primary**
To describe the safety and tolerability of [RSVpreF+BNT162b2]	In participants receiving study intervention, the percentage of participants reporting: • Local reactions within 7 days following vaccination • Systemic events within 7 days following vaccination • AEs from vaccination through 1 month after vaccination • SAEs from vaccination through 6 months after vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To demonstrate that the immune responses elicited by [RSVpreF+BNT162b2] when coadministered with QIV are noninferior to those elicited by each vaccine alone: 1. RSVpreF alone (Group 1 vs Group 4)	1. In participants in compliance with the key protocol criteria (evaluable participants for Groups 1 and 4): • GMR of NTs at 1 month after vaccination in Group 1 to Group 4 for RSV subgroup A • GMR of NTs at 1 month after vaccination in Group 1 to Group 4 for RSV subgroup B	1. RSV A and RSV B NTs
2. Bivalent BNT162b2 alone (Group 1 vs Group 3)	2. In participants in compliance with the key protocol criteria (evaluable participants for Groups 1 and 3): • GMR of NTs at 1 month after vaccination in Group 1 to Group 3 for SARS-CoV-2 Omicron BA.4/BA.5 • GMR of NTs at 1 month after vaccination in Group 1 to Group 3 for SARS-CoV-2 reference strain	2. SARS-CoV-2 Omicron BA.4/BA.5 and reference-strain NTs
3. QIV alone (Group 1 vs Group 5)	3. In participants in compliance with the key protocol criteria (evaluable participants for Groups 1 and 5): • GMR of HAI titers at 1 month after vaccination in Group 1 to Group 5 for each influenza strain included in the QIV	3. HAI titers for each strain contained in the QIV

Substudy A (Phase 1/2)		
Objectives	**Estimands**	**Endpoints**
To demonstrate that the immune responses elicited by [RSVpreF+BNT162b2] are noninferior to those elicited by each vaccine alone: 1. RSVpreF alone (Group 2 vs Group 4)	1. In participants in compliance with the key protocol criteria (evaluable participants for Groups 2 and 4): • GMR of NTs at 1 month after vaccination in Group 2 to Group 4 for RSV subgroup A • GMR of NTs at 1 month after vaccination in Group 2 to Group 4 for RSV subgroup B	1. RSV A and RSV B NTs
2. Bivalent BNT162b2 alone (Group 2 vs Group 3)	2. In participants in compliance with the key protocol criteria (evaluable participants for Groups 2 and 3): • GMR of NTs at 1 month after vaccination in Group 2 to Group 3 for SARS-CoV-2 Omicron BA.4/BA.5 • GMR of NTs at 1 month after vaccination in Group 2 to Group 3 for SARS-CoV-2 reference strain	2. SARS-CoV-2 Omicron BA.4/BA.5 and reference-strain NTs
Secondary	**Secondary**	**Secondary**
To demonstrate that the immune responses elicited by RSVpreF, bivalent BNT162b2, and QIV, when administered concomitantly, are noninferior to those elicited by each vaccine alone: 1. RSVpreF (Group 7 vs Group 4)	1. In participants in compliance with the key protocol criteria (evaluable participants for Groups 7 and 4): • GMR of NTs at 1 month after vaccination in Group 7 to Group 4 for RSV subgroup A • GMR of NTs at 1 month after vaccination in Group 7 to Group 4 for RSV subgroup B	1. RSV A and RSV B NTs
2. Bivalent BNT162b2 (Group 7 vs Group 3)	2. In participants in compliance with the key protocol criteria (evaluable participants for Groups 7 and 3): • GMR of NTs at 1 month after vaccination in Group 7 to Group 3 for SARS-CoV-2 Omicron BA.4/BA.5 • GMR of NTs at 1 month after vaccination in Group 7 to Group 3 for SARS-CoV-2 reference strain	2. SARS-CoV-2 Omicron BA.4/BA.5 and reference-strain NTs

Substudy A (Phase 1/2)		
Objectives	**Estimands**	**Endpoints**
3. QIV (Group 7 vs Group 5)	3. In participants in compliance with the key protocol criteria (evaluable participants for Groups 7 and 5): • GMR of NTs at 1 month after vaccination in Group 7 to Group 5 for each influenza strain included in the QIV	3. HAI titers for each strain contained in the QIV
To demonstrate that the immune responses elicited by RSVpreF and bivalent BNT162b2 when administered concomitantly are noninferior to those elicited by each vaccine alone: 1. RSVpreF (Group 6 vs Group 4)	1. In participants in compliance with the key protocol criteria (evaluable participants for Groups 6 and 4): • GMR of NTs at 1 month after vaccination in Group 6 to Group 4 for RSV subgroup A • GMR of NTs at 1 month after vaccination in Group 6 to Group 4 for RSV subgroup B	1. RSV A and RSV B NTs
2. Bivalent BNT162b2 (Group 6 vs Group 3)	2. In participants in compliance with the key protocol criteria (evaluable participants for Groups 6 and 3): • GMR of NTs at 1 month after vaccination in Group 6 to Group 3 for SARS-CoV-2 Omicron BA.4/BA.5 • GMR of NTs at 1 month after vaccination in Group 6 to Group 3 for SARS-CoV-2 reference strain	2. SARS-CoV-2 Omicron BA.4/BA.5 and reference-strain NTs
Exploratory	**Exploratory**	**Exploratory**
To further describe the immune responses elicited by [RSVpreF+BNT162b2]	NA	NA

10.11.6. Substudy A Design

10.11.6.1. Overall Design

This is a Phase 1/2 randomized, parallel-group, observer-blinded substudy to describe the safety, tolerability, and immunogenicity of a combined RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine [RSVpreF+BNT162b2], administered concomitantly with a seasonal influenza vaccine or administered alone. Approximately 1050 healthy participants ≥65 years of age will be enrolled in Substudy A.

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

Randomization will be conducted across 2 enrollment strata (see Table 4).

Table 4. Substudy A Enrollment Strata

Enrollment Stratum	Total Number of Participants	Number of Participants per Vaccine Group	Vaccine Group Number	Vaccine Group Description
1	750	150	1	[RSVpreF+BNT162b2] administered concurrently in the opposite arm to licensed QIV
		150	2	[RSVpreF+BNT162b2] administered concurrently in the opposite arm to placebo
		150	3	Bivalent BNT162b2 administered concurrently in the opposite arm to placebo
		150	4	RSVpreF administered concurrently in the opposite arm to placebo
		150	5	Licensed QIV administered concurrently in the opposite arm to placebo
2	300	150	6	RSVpreF and bivalent BNT162b2 (2 injections in the same arm) coadministered concurrently in the opposite arm to placebo
		150	7	RSVpreF and bivalent BNT162b2 (2 injections in the same arm) coadministered concurrently in the opposite arm to QIV

All participants will be asked to complete a reactogenicity e-diary for 7 days following vaccination. Blood samples of approximately 50 mL will be collected for immunogenicity assessments prior to vaccination at Visit A101 and 1 month after vaccination (Visit A102).

E-diary data from Day 1 through Day 3 for the first 50 participants in Groups 1 to 5, and the first 20 participants in Groups 6 and 7, will be evaluated prior to enrollment of the remaining participants in each group.

AEs and SAEs will be collected from the signing of informed consent through Visit A102 (1-month follow-up visit). SAEs will be collected from the signing of informed consent through Visit A103 (6-month telephone contact).

Substudy A will have stopping rules that will apply to participants as detailed in Section 10.11.10.5, with monitoring by designated unblinded sponsor site staff on an ongoing basis. If a stopping rule is confirmed, further randomization and study intervention administration will be paused while additional information is gathered, and cumulative unblinded safety data will be reviewed by the IRC. Participants who have received study intervention will continue further study visits and procedures as scheduled. A charter for the IRC will be prepared and finalized before the first participant provides informed consent.

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

10.11.6.2. Scientific Rationale for Study Design

See Section 2.1.

10.11.6.3. Justification for Dose

See Section 4.3.

10.11.6.4. End of Study Definition

See Section 4.4.

10.11.7. Substudy A Population

10.11.7.1. Substudy A Inclusion Criteria

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

Age and Sex:

1. Male or female participants ≥65 years of age at Visit 1 (Day 1).

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

Disease Characteristics:

NA.

Other Inclusion Criteria:

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

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

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

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

5. Participants who have received at least 3 prior US-authorized mRNA COVID-19 vaccines, with the last dose being an updated (bivalent) vaccine given at least ≥150 days before Visit A101 (Day 1). Any dose of modRNA SARS-CoV-2 vaccine received after 01 September 2022 in the US may be considered to be a bivalent vaccine.

   Note: Documented confirmation of prior doses of COVID-19 vaccines received must be obtained prior to randomization.

10.11.7.2. Substudy A Exclusion Criteria

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

Medical Conditions:

1. A confirmed diagnosis of COVID-19, RSV infection, or influenza ≤120 days before study intervention administration.

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

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

6. 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.

Prior/Concomitant Therapy:

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

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

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

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

10. Receipt of any influenza vaccine ≤120 days before study enrollment.

Prior/Concurrent Clinical Study Experience:

11. Participation in other studies involving a study intervention within 28 days before randomization.

12. Anticipated participation in other studies within 28 days after receipt of study intervention in this study.

Diagnostic Assessments:

NA.

Other Exclusion Criteria:

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

10.11.7.3. 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 considered eligible. Participants meeting these criteria at Visit 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

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

2. Current febrile illness (oral temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study intervention administration. This includes symptoms that could represent a potential COVID-19 illness (refer to Section 8.4.8).

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

3. Receipt of any nonstudy vaccine within 28 days before study intervention administration at Visit A101.

4. Anticipated receipt of any nonstudy vaccine within 28 days after study intervention administration at Visit A101.

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

10.11.8. Substudy A Intervention 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.

- Combined RSVpreF and bivalent BNT162b2 (original*/Omi BA.4/BA.5) vaccine [RSVpreF+BNT162b2] 0.8 mL, which is a combination of the following:
  - 120 µg RSVpreF containing 2 stabilized RSV prefusion F antigens, in equal amounts (60 µg per strain) from virus subgroups A and B
  - 30 µg Bivalent BNT162b2 (15 µg original/Omi BA.4/BA.5), which contains original BNT162b2 and BNT162b2 Omicron (15 µg B.1.1.529 sublineage BA.4/BA.5)

- 120 µg RSVpreF containing 2 stabilized RSV prefusion F antigens, in equal amounts (60 µg per strain) from virus subgroups A and B
- Licensed QIV
- 30 µg Bivalent BNT162b2 (15 µg original/Omi BA.4/BA.5), which contains original BNT162b2 and BNT162b2 Omicron (15 µg B.1.1.529 sublineage BA.4/BA.5)
- Normal saline (0.9% sodium chloride solution for injection) 0.8 mL

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

10.11.8.1. Study Intervention(s) Administered

Study interventions for Substudy A will include the following:

Substudy A Study Interventions					
Intervention Name	**Combination [RSVpreF+BNTb162b2]**	**Bivalent BNT162b2 (Original[a]/Omi BA.4/BA.5)**	**RSVpreF**	**QIV**	**Normal Saline Placebo**
Arm Name (group of participants receiving a specific study intervention or no study intervention)	Groups 1, 2: Combination [RSVpreF+BNT162b2]	Groups 3, 6, 7: Bivalent BNT162b2 (original[a]/Omi BA.4/BA.5) (30 µg)	Groups 4, 6, 7: RSVpreF (120 µg)	Groups 1, 5, 7: QIV	Groups 2, 3, 4, 5, 6: Placebo
Targeted Influenza Strains	NA	NA	NA	For each season, strains as recommended by WHO	NA
Type	Vaccine	modRNA vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	Suspension for injection	Suspension for injection	Powder for solution for injection	Suspension for injection	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	As detailed in the IPM	As detailed in the IPM	As detailed in the IPM	As detailed in the IPM	NA
Dosage Level(s) or Volume	RSVpreF 120 µg Bivalent BNT162b2 30 µg	30 µg	120 µg	0.7 mL	0.8 mL
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Comparator (Group 3) Experimental (Groups 6 and 7)	Comparator (Group 4) Experimental (Groups 6 and 7)	Comparator (Group 5) Experimental (Groups 1 and 7)	Placebo for blinding
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by Pfizer	Provided centrally by Pfizer	Provided centrally by Pfizer	Provided centrally by Pfizer	Provided centrally by Pfizer

Substudy A Study Interventions					
Intervention Name	**Combination [RSVpreF+BNTb162b2]**	**Bivalent BNT162b2 (Original[a]/Omi BA.4/BA.5)**	**RSVpreF**	**QIV**	**Normal Saline Placebo**
Packaging and Labeling	Study intervention will be generated by mixing the following at the site at the dose-level combinations detailed below: • RSVpreF • Bivalent BNT162b2 (original[a]/Omi BA.4/BA.5) Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled per country requirement.	Study intervention will be provided in a glass vial as open-label supply. It is reconstituted with a PFS of sterile water diluent for injection (supplied). Each vial and PFS will be labeled per country requirement.	Study intervention will be provided as a PFS as open-label supply. Each carton will be labeled per country requirement.	Study intervention will be provided as either a PFS or a glass/plastic vial as open-label supply. Each PFS or vial will be labeled per country requirement.
SRSD	IB	IB	IB	USPI	NA

a. Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020).

Substudy A Study Arms							
Group Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Arm Title	Combination [RSVpreF+BNT162b2 (0.8 mL)] + QIV	Combination [RSVpreF+BNT162b2 (0.8 mL)] + placebo	Bivalent BNT162b2 (30 µg) + placebo	RSVpreF (120 µg) + placebo	QIV + placebo	Coadministration RSVpreF + bivalent BNT162b2 + placebo	Coadministration RSVpreF + bivalent BNT162b2 + QIV
Arm Type	Experimental	Experimental	Comparator	Comparator	Comparator	Experimental	Experimental
Arm Description	Participants will receive combination [RSVpreF (120 µg) + BNT162b2 (30 µg)] + QIV	Participants will receive combination [RSVpreF (120 µg) + BNT162b2 (30 µg)] + placebo	Participants will receive BNT162b2 (30 µg) + placebo	Participants will receive RSVpreF (120 µg) + placebo	Participants will receive QIV + placebo	Participants will receive coadministered RSVpreF (120 µg) + BNT162b2 (30 µg) + placebo	Participants will receive coadministered RSVpreF (120 µg) + BNT162b2 (30 µg) + QIV

Substudy A Study Arms							
Group Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Associated Intervention Labels	[RSVpreF (120 µg) + BNT162b2 (30 µg)] + QIV	[RSVpreF (120 µg) + BNT162b2 (30 µg)] + placebo	BNT162b2 (30 µg) + placebo	RSVpreF (120 µg) + placebo	QIV + placebo	RSVpreF (120 µg) + BNT162b2 (30 µg) + placebo	RSVpreF (120 µg) + BNT162b2 (30 µg) + QIV

10.11.8.1.1. Administration

See Section 10.11.8.1.

During Substudy A, all study interventions are to be administered as an intramuscular injection into the deltoid muscle of the arm, in accordance with the schema (Section 10.11.2) and the SoA (Section 10.11.3).

10.11.8.1.2. Medical Devices

See Section 6.1.2.

10.11.8.1.3. Preparation, Handling, Storage, and Accountability

See Section 6.2.

10.11.8.1.3.1. Preparation and Dispensing

See Section 6.2.1.

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

10.11.8.1.4. Allocation to Study Intervention

See Section 6.3.

Allocation of study intervention at Visit A101 in Substudy A will be conducted via the IRT.

E-diary data from Day 1 through Day 3 for the first 50 participants in Groups 1 to 5, and the first 20 participants in Groups 6 and 7, will be evaluated prior to enrollment of the remaining participants in each group. Initial enrollment will be controlled through the IRT system to manage this approach.

10.11.8.2. Blinding

This is an observer-blinded study.

10.11.8.2.1. Blinding of Participants

Participants will be blinded to their assigned study intervention. When the 1-month analysis has been performed, and when directed by the sponsor (anticipated to be between Visit A102 and Visit A103), participants may be unblinded to confirm the vaccine received. The study team will also become unblinded to the participant's study intervention allocation at this time.

10.11.8.2.2. Blinding of Site Personnel

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

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

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

10.11.8.2.3. Blinding of the Sponsor

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.

- An unblinded team will support interactions with and analyses for the IRC (see Section 10.1.5). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.

When the 1-month analysis has been performed, and when directed by the sponsor (anticipated to be between Visit A102 and Visit A103), participants may be unblinded to confirm the vaccine received. The study team will also become unblinded to the participant's study intervention allocation at this time.

10.11.8.2.4. Breaking the Blind

See Section 6.4.4.

10.11.8.3. Study Intervention Compliance

See Section 6.5.

10.11.8.4. Dose Modification

NA.

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

See Section 6.7.

10.11.8.6. Treatment of Overdose

See Section 6.8.

10.11.8.7. Prior and Concomitant Therapy

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

- Prior receipt of any COVID-19 vaccine.
- Influenza vaccine*, if received during the 12 months prior to enrollment.
    - *Include product name and date of administration.
- Any vaccinations received from 28 days prior to study enrollment until the last visit (A103).
- Prohibited medications listed in Section 10.11.8.7.1, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

10.11.8.7.1. Prohibited During the Study

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

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after study vaccination at Visit 1.
- Licensed or nonstudy investigational coronavirus vaccine from enrollment through 31 August 2023.
- Licensed or nonstudy investigational influenza vaccine from enrollment through 31 August 2023.
- Licensed or nonstudy investigational RSV vaccine from enrollment through 31 August 2023.
- Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study is prohibited.
- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment through 28 days after administration of the study intervention.
- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies, from 60 days before study intervention administration through conclusion of the study.
- Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

10.11.8.7.2. Permitted During the Study

- Medication other than that described as prohibited in Section 10.11.8.7.1 required for treatment of preexisting conditions or acute illness is permitted.
- Inhaled, topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

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

See Section 7.

10.11.10. Substudy A Assessments and Procedures

For Substudy A, the minimal blood sampling volume for all individual participants in this study is approximately 100 mL.

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

10.11.10.1. Immunogenicity Assessments

Samples will be collected at time points as specified in Section 10.11.3 from all applicable participants, and the following assays will be performed:

- HAI titers for the matched seasonal strains (2×A, 2×B) recommended by WHO for Groups 1, 5, and 7.
- SARS-CoV-2 neutralization assay (reference strain) for Groups 1, 2, 3, 6, and 7.
- SARS-CoV-2 neutralization assays (Omicron BA.4, Omicron BA.5; other variants, including other Omicron sublineages, may also be evaluated) for Groups 1, 2, 3, 6, and 7.
- RSV A and RSV B serum NTs for Groups 1, 2, 4, 6, and 7.

10.11.10.2. N-Binding Antibody Test

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

10.11.10.3. Biological Samples

See Section 8.2.1.

10.11.10.4. Safety Assessments

See Section 8.3.

10.11.10.5. Stopping Rules

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

- The IRC will review all appropriate data.
    - The stopping rule will PAUSE randomization and any further study intervention administration.

- For all participants already vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following criteria occur within 28 days after study intervention administration.

Stopping Rule Criteria:

If any participant vaccinated with the combined RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine [RSVpreF+BNT162b2] develops:

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

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

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

3. If ≥1 participant vaccinated with any [RSVpreF+BNT162b2] combination develops confirmed myocarditis or pericarditis.

4. If any participant vaccinated with any [RSVpreF+BNT162b2] combination dies.

A charter for the IRC will be prepared and finalized before the first participant provides consent.

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

See Section 8.4.

10.11.10.7. Study Procedures

10.11.10.7.1. Visit A101 – 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 their designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

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

- Assign a participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected (as permitted by local regulations) to critically evaluate the immune response and safety profile by age.
- Obtain medical history data*, including confirmed COVID-19 diagnosis (see Section 8.4.8) or asymptomatic positive SARS-CoV-2 test result (NAAT or antigen test), and any other medical history of clinical significance.
    - *Include date of onset and resolution (if applicable).
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF or on the AE CRF as per Section 10.3.
- Measure the participant's height and weight.
- Measure the participant's vital signs, including oral temperature, pulse rate, and seated blood pressure.
- Discuss contraceptive use as described in Section 5.3.1.
- Review documentation of all prior COVID-19 vaccinations. Record prior receipt of any COVID-19 vaccine as described in Section 10.11.8.7.
- Record details of any influenza vaccine received in the prior 12 months, as described in Section 10.11.8.7.
- Record nonstudy vaccinations as described in Section 10.11.8.7.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system.
- Collect a blood sample (approximately 50 mL), before administration of study intervention, for immunogenicity assessment.

- Unblinded site staff member(s) will dispense/administer study intervention into the deltoid muscle of the arm as described in Section 10.11.8. Please refer to the IPM for further instruction on this process.

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

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

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

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Record AEs as described in Section 8.4.1.

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

- Ask the participant to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.11.10.7.5).

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

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and updates the study intervention accountability records.

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

10.11.10.7.2. Visit A102 – 1-Month Follow-Up Visit (After Vaccination) – 28 to 35 Days After Visit A101

- Record AEs as described in Section 8.4.

- Record nonstudy vaccinations as described in Section 10.11.8.7.

- Record prohibited medication use as described in Section 10.11.8.7.1.

- Verify understanding of and compliance with protocol requirements for contraception as described in Section 5.3.1.

- Collect a blood sample of approximately 50 mL for immunogenicity testing.

- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- If not already completed, collect the participant's e-diary or assist the participant with removing the study application from their own personal device.

    - Ensure all e-diary data have been transferred prior to e-diary deactivation or removal of the app.

- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.4.1.

10.11.10.7.3. Visit A103 – 6-Month Telephone Contact – 175 to 189 Days After Visit A101

- Contact the participant by telephone.

- Record SAEs as described in Section 8.4.

- Record nonstudy vaccinations as described in Section 10.11.8.7.

- Record prohibited medication use as described in Section 10.11.8.7.1.

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

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

If a Grade 3 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever of ≥39.0°C (≥102.1°F) (Section 8.3.4.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever (Section 8.3.4.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets Grade 4 criteria.

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

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

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

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

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

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.3.4.2.

- Assess systemic events (if present) in accordance with the grades provided in Section 8.3.4.3.
- Assess other findings associated with the reaction and record this on the AE page of the CRF if appropriate.
- The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

10.11.10.7.5. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 28 days after study vaccination must be specifically evaluated for possible myocarditis or pericarditis.

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

- ECG and
- Measurement of the troponin level

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

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

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

10.11.11. Statistical Considerations – Substudy A

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

10.11.11.1. Statistical Hypotheses

The estimands corresponding to the primary and secondary objectives are described in the table in Section 10.11.5.

Both primary and secondary immunogenicity objectives are hypothesis-testing objectives. The subsections below describe details of hypotheses to be tested for each objective.

10.11.11.1.1. Statistical Hypotheses for Combined Vaccine Coadministered With QIV

A total of 8 hypotheses will be tested for the first primary immunogenicity objective as described below for each vaccine component.

1. The null hypothesis (H_0) to assess noninferiority of the response with respect to RSVpreF will be evaluated by the following hypothesis for both RSV A and RSV B as measured by NT:

   H_0: $\ln(\mu_1) - \ln(\mu_4) \leq \ln(0.5)$

   where ln(0.5) corresponds to a 2-fold margin for noninferiority, and $\ln(\mu_1)$ and $\ln(\mu_4)$ are the natural log of the geometric mean of NT at 1 month after vaccination for Group 1 and Group 4, respectively.

2. The null hypothesis (H_0) to assess noninferiority of the response with respect to BNT162b2 will be evaluated by the following hypothesis for both the SARS-CoV-2 Omicron BA.4/BA.5 strain and the reference strain as measured by NT:

   H_0: $\ln(\mu_1) - \ln(\mu_3) \leq \ln(0.5)$

   where ln(0.5) corresponds to a 2-fold margin for noninferiority, and $\ln(\mu_1)$ and $\ln(\mu_3)$ are the natural log of the geometric mean of NT at 1 month after vaccination for Group 1 and Group 3, respectively.

3. The null hypothesis (H_0) to assess noninferiority of the response with respect to QIV will be evaluated by the following hypothesis for each of the 4 strains included in QIV as measured by HAI titer:

   H_0: $\ln(\mu_1) - \ln(\mu_5) \leq \ln(0.5)$

   where ln(0.5) corresponds to a 2-fold margin for noninferiority, and $\ln(\mu_1)$ and $\ln(\mu_5)$ are the natural log of the geometric mean of HAI titers at 1 month after vaccination for Group 1 and Group 5, respectively.

10.11.11.1.2. Statistical Hypotheses for Combined Vaccine Alone

A total of 4 hypotheses will be tested for the second primary immunogenicity objective as described below for each vaccine component.

1. The null hypothesis (H_0) to assess noninferiority of the response with respect to RSVpreF will be evaluated by the following hypothesis for both RSV A and RSV B as measured by NT:

   H_0: $\ln(\mu_2) - \ln(\mu_4) \leq \ln(0.5)$

   where ln(0.5) corresponds to a 2-fold margin for noninferiority and $\ln(\mu_2)$ and $\ln(\mu_4)$ are the natural log of the geometric mean of NT at 1 month after vaccination for Group 2 and Group 4, respectively.

2. The null hypothesis (H_0) to assess noninferiority of the response with respect to BNT162b2 will be evaluated by the following hypothesis for both the SARS-CoV-2 Omicron BA.4/BA.5 strain and the reference strain as measured by NT:

   H_0: $\ln(\mu_2) - \ln(\mu_3) \leq \ln(0.5)$

   where ln(0.5) corresponds to a 2-fold margin for noninferiority and $\ln(\mu_2)$ and $\ln(\mu_3)$ are the natural log of the geometric mean of NT at 1 month after vaccination for Group 2 and Group 3, respectively.

10.11.11.1.3. Statistical Hypotheses for Coadministration of 3 Individual Vaccines

A total of 8 hypotheses will be tested for the first of the secondary objectives similar to Section 10.11.11.1.1, except that Group 1 will be replaced with Group 7.

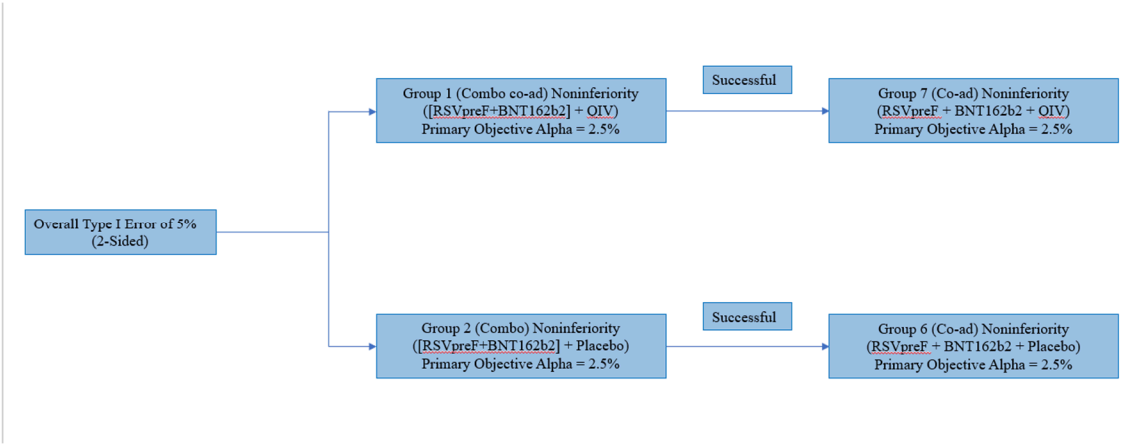
10.11.11.1.4. Statistical Hypotheses for Coadministration of 2 Individual Vaccines

A total of 4 hypotheses will be tested for the second of the secondary objectives similar to Section 10.11.11.1.2, except that Group 2 will be replaced with Group 6.

10.11.11.1.5. Multiplicity Adjustment

Type I error of 5% is equally split between the 2 primary immunogenicity objectives (2-sided 2.5% for each). The first primary immunogenicity objective will be achieved if all 8 null hypotheses are rejected. The second primary immunogenicity objective will be achieved if all 4 null hypotheses are rejected. The study is considered successful if either primary immunogenicity objective is achieved.

The secondary immunogenicity objectives will be tested sequentially after the primary objective(s) is achieved as described in the schema below.



10.11.11.2. Analysis Sets

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

Population	Description
Enrolled	All participants who sign the ICD.
Randomized population	All participants who are assigned a randomization number in the IWR system regardless of whether the study intervention was administered.
Safety population	All participants who receive the study intervention.
mITT immunogenicity population	All randomized participants who receive the study intervention and have at least 1 valid and determinate assay result after vaccination.
Evaluable immunogenicity population	All participants who are eligible, receive the study intervention to which they were randomized, have the 1-month postvaccination blood collection within an appropriate window, have no major protocol violations from randomization through the 1-month postvaccination blood draw, and have at least 1 valid and determinate assay result at the 1-month postvaccination visit.

10.11.11.3. Statistical Analyses

10.11.11.3.1. General Considerations

Refer to Section 9 for general considerations of statistical analyses.

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

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint in each vaccine group (Group 1 to Group 7 individually). Local reactions (pain at the injection site, redness, and swelling) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) from Day 1 through Day 7 after vaccination will be presented by maximum severity and any severity. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs (Section 9.3.1). • AEs and SAEs will be categorized according to MedDRA terms. All of the AEs reported through the 1-month follow-up visit and SAEs reported throughout the study will be descriptively summarized with counts, percentages, and associated Clopper-Pearson 95% CI for each vaccine group (Section 9.3.1).
Immunogenicity	• GMRs of RSV A and RSV B NTs (Group 1 to Group 4), GMRs of SARS-CoV-2 Omicron BA.4/BA.5–strain NTs and reference-strain NTs (Group 1 to Group 3), influenza strain-specific GMRs of HAI titers (Group 1 to Group 5) at 1 month after vaccination will be provided with 97.5% CIs (Section 9.3.1.2.3). Using a 2-fold noninferiority margin, success for the first primary immunogenicity objective will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5 for both RSV A and RSV B antigens, for both the Omicron BA.4/BA.5 and reference strains, and for all 4 QIV strains. • GMRs of RSV A and RSV B NTs (Group 2 to Group 4) and GMRs of SARS-CoV-2 Omicron BA.4/BA.5–strain NTs and reference-strain NTs (Group 2 to Group 3) at 1 month after vaccination will be provided with 97.5% CIs (Section 9.3.1.2.3). Using a 2-fold noninferiority margin, success for the second primary immunogenicity objective will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5 for both RSV A and RSV B antigens and for both the Omicron BA.4/BA.5 and reference strains.

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

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	• GMRs of RSV A and RSV B NTs (Group 7 to Group 4), GMRs of SARS-CoV-2 Omicron BA.4/BA.5–strain NTs and reference-strain NTs (Group 7 to Group 3), influenza strain-specific GMRs of HAI titers (Group 7 to Group 5) at 1 month after vaccination will be provided with 97.5% CIs (Section 9.3.1.2.3). Using a 2-fold noninferiority margin, success for the first of the secondary immunogenicity objectives will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5 for both RSV A and RSV B antigens, for both the Omicron BA.4/BA.5 and reference strains, and for all 4 QIV strains, after the first primary immunogenicity objective is achieved. • GMRs of RSV A and RSV B NTs (Group 6 to Group 4) and GMRs of SARS-CoV-2 Omicron BA.4/BA.5–strain NTs and reference-strain NTs (Group 6 to Group 3) at 1 month after vaccination will be provided with 97.5% CIs (Section 9.3.1.2.3). Using a 2-fold noninferiority margin, success for the second of the secondary immunogenicity objectives will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5 for both RSV A and RSV B antigens and for both the Omicron BA.4/BA.5 and reference strains, after the second primary immunogenicity objective is achieved.

10.11.11.3.4. Exploratory Endpoint(s) Analysis

Endpoint	Statistical Analysis Methods
Exploratory	• GMTs of NTs for each RSV subgroup (A or B), GMTs of QIV strain-specific HAI titers, and GMTs of SARS-CoV-2 strain–specific NTs will be descriptively summarized with 2-sided 95% CIs for each applicable vaccine group both before vaccination and at the 1-month postvaccination visit (Section 9.3.1). • GMFRs of NTs for each RSV subgroup (A or B), GMFRs of influenza strain-specific HAI titers, and GMFRs of SARS-CoV-2 strain–specific NTs from before vaccination to the 1-month postvaccination visit will be descriptively summarized with 2-sided 95% CIs for each applicable vaccine group (Section 9.3.1).

Endpoint	Statistical Analysis Methods
	• The number and percentage of participants achieving strain-specific HAI seroconversion, SARS-CoV-2 strain–specific seroresponse at 1 month after vaccination, and the number and percentage of participants with strain-specific HAI titers ≥1:40 before vaccination and 1 month after vaccination will be summarized with 2-sided Clopper-Pearson 95% CIs for each applicable vaccine group (Section 9.3.1). Note: HAI seroconversion is defined as an HAI titer <1:10 prior to vaccination and ≥1:40 at the postvaccination visit, or an HAI titer of ≥1:10 prior to vaccination with a 4-fold rise at the postvaccination visit. SARS-CoV-2 seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse. • GMTs may be compared between other vaccine groups (eg, Group 1 vs Group 2; Group 1 vs Group 7; Group 2 vs Group 6; etc) with GMRs and associated 2-sided 95% CIs (Section 9.3.1.2.3).

10.11.11.4. Interim Analyses

No formal interim analysis will be conducted for this study phase.

The primary analysis will be performed on safety and immunogenicity data through 1 month after vaccination (ie, Visit A102); all type I error will be spent at this analysis. Once this analysis has been completed, study participants and the study team may be unblinded to study intervention allocation.

6-Month safety data will be summarized when they become available.

10.11.11.5. Sample Size Determination

Table 5 presents the power to demonstrate the noninferiority for each antigen included in Group 1 ([RSVpreF+BNT162b2] + QIV) as well as the power to demonstrate the noninferiority for each antigen included in Group 2 ([RSVpreF+BNT162b2] + placebo). The power for the secondary objectives is similar to that for the primary objectives as the comparisons and assumptions are similar.

For all assay results, no interference is assumed (ie, GMR=1). The SDs of the log titers are based on different reference studies. With 135 evaluable participants per vaccine group, there is ~90% power to declare noninferiority for all 8 antigens included in Group 1, and ~92% power to declare noninferiority for all 4 antigens included in Group 2. Power was calculated with PROC POWER in SAS using the TWOSAMPLEMEANS statement. Assuming 10% of the participants are nonevaluable, approximately 150 participants per group need to be enrolled for Groups 1 through 7.

Table 5. Power to Demonstrate Noninferiority (N=135 per Group)

Vaccine Component (SD Reference Study)	Antigen/Endpoint	Common SD (Log e Scale)	Difference (Log e Scale)	Noninferiority Margin	Power to Declare Noninferiority (1-Sided Alpha = 0.0125)
RSVpreF (C3671013)	RSV A NT	1.1	0	2-Fold	99.8%
	RSV B NT	1.1	0	2-Fold	99.8%
BNT162b2 (C4591044)	SARS-CoV-2 Omicron BA.4/BA.5–strain NTs	1.5	0	2-Fold	93.8%
	SARS-CoV-2 reference-strain NTs	1.3	0	2-Fold	98.3%
QIV (C3671006)	H1N1 HAI	1.1	0	2-Fold	99.8%
	H3N2 HAI	1.1	0	2-Fold	99.8%
	B strain 1 HAI	1.2	0	2-Fold	99.3%
	B strain 2 HAI	1.2	0	2-Fold	99.3%
Overall power to reject all 8 tests (Group 1 or 7 vs Group 4, Group 1 or 7 vs Group 3, Group 1 or 7 vs Group 5)					90.2%
Overall power to reject all first 4 tests (Group 2 or 6 vs Group 4, Group 2 or 6 vs Group 3)					91.8%

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:

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Added Substudy B	New substudy on alternative formulation of RSVpreF and BNT162b2 (Omi XBB.1.5) combination vaccine [RSVpreF+BNT162b2]	Section 10.12 Appendix 12: Substudy B (Phase 1/2)
Non-substantial Modification(s)		
Updated/removed text in the body of protocol that was specific to Substudy A	Substudy-specific text is included in substudy appendices	Section 1.1 Synopsis Section 2.3.1 Risk Assessment Section 7.2 Participant Discontinuation/Withdrawal From the Study Section 5.4 Screen Failures Section 8.3.1 Physical Examinations Section 8.3.2 Vital Signs Section 8.3.3 Clinical Safety Laboratory Assessments Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information Section 8.4.8 Adverse Events of Special Interest for Substudy A Section 10.11.4 Introduction – Substudy A
Updated references and text to include Substudy B	Changes to align with master protocol format	Sections 1 through 9 Section 10.1.5.1 Data Monitoring Committee Section 10.2 Appendix 2: Clinical Laboratory Tests Section 10.5 Appendix 5: Genetics

Description of Change	Brief Rationale	Section # and Name
Added stopping rule text for Substudy B	Consistency with Substudy A	Section 1.1 Synopsis
Added IND number and clintrials.gov ID	Not available at the time of original protocol	Title page Section 1.1 Synopsis
Updated text on anaphylaxis and myocarditis assessment for RSVpreF	Consolidated the risk text from RSV and COVID; updated based on the recent updates for both programs	Section 2.3.1 Risk Assessment
Removed text on bivalent BNT162b2 vaccine approval	Updated formulation	Section 2.2.3.1 SARS-CoV-2
Removed collection of date of birth	New requirement	Section 8.1 Administrative Procedures
Added instructions for noting COVID-19 symptoms for Substudy A	Editorial change	Section 10.11.3 SoA – Substudy A
"RSV" was updated to "RSVpreF" as per PACL (26 April 2023)	Correction of typographical error	Section 2.3 Benefit/Risk Assessment
Updated information on RSVpreF	Introductory paragraph on clinical studies	Section 2.2.3.2 RSVpreF Vaccination
Added/updated text Substudy B formulation to read "alternative formulation of RSVpreF and BNT162b2 (Omi XBB.1.5) combination vaccine [RSVpreF+BNT162b2]"	Consistency throughout the document	Section 1: Protocol Summary Section 4.3: Justification for Dose Section 10.12 Appendix 12: Substudy B Section 10.13 Appendix 13: Abbreviations
Added a review of e-diary data from Days 1 through 3 for the first 50 participants in Stratum 1 and the first	Regulatory recommendation since there is no prior human experience with the combined RSVpreF and	Section 10.11.6.1 Overall Design Section 10.11.8.1.4 Allocation to Study Intervention

Description of Change	Brief Rationale	Section # and Name
20 participants in Stratum 2 prior to enrollment of the remaining participants in each group per PACL (01 June 2023)	bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine	
Stopping rule #2 updated from "troponin I" to "troponin" per PACL (12 July 2023)	To accommodate sites not able to measure troponin I	Section 10.11.10.5 Stopping Rules
"Licensed influenza vaccine" updated to "influenza vaccine" per PACL (12 July 2023)	To accommodate participants that may have received investigational influenza vaccines	Section 10.11.3 SoA – Substudy A (Phase 1/2) Section 10.11.8.7 Prior and Concomitant Therapy Section 10.11.10.7 Study Procedures
Added volume for normal saline placebo per PACL (26 April 2023)	Addition of text that was inadvertently omitted in original protocol	Section 10.11.8 Substudy A Intervention and Concomitant Therapy Section 10.11.8.1 Study Intervention(s) Administered
Added volume for QIV	Addition of text that was inadvertently omitted in original protocol	Section 10.11.8.1 Study Intervention(s) Administered
Updated barrier requirements	New information for Comirnaty and Abrysvo	Section 4.2.3 Choice of Contraception/Barrier Requirements
Removed text inadvertently included previously	Typographical errors corrected	Section 10.11.7.3 Study Procedures Section 10.11.11.2 Analysis Sets Section 10.11.11.3 Statistical Analyses

10.13. Appendix 13: Abbreviations

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
ARI-RSV	RSV-associated acute respiratory illness
AST	aspartate aminotransferase
AV	atrioventricular
AxMP	auxiliary medicinal product
BNT162b2	Pfizer's 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)
ChAdOx1-S	ChAdOx1-S (recombinant) SARS-CoV-2 vaccine (AstraZeneca)
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CpG	CpG 24555
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CTIS	Clinical Trial Information System
DCT	data collection tool
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding

Abbreviation	Term
e-diary	electronic diary
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
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
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
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
HD	high dose
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IPAL	investigational product accountability log
IPM	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISO	International Organization for Standardization

Abbreviation	Term
IV	intravenous(ly)
IWR	interactive Web-based response
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LRTI	lower respiratory tract illness
LRTI-RSV	RSV-associated lower respiratory tract illness
LSLV	last subject last visit
MDR	medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
mRNA	messenger ribonucleic acid
mRNA-1273	mRNA-1273 SARS-CoV-2 vaccine (Moderna)
NA	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
NIMP	noninvestigational medicinal product
NT	neutralizing titer
Omi	Omicron
PACL	protocol administrative change letter
PFS	prefilled syringe(s)
PI	principal investigator
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
QIV	quadrivalent influenza vaccine
QTcF	QT interval corrected by the Fridericia formula
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
[RSVpreF+BNT162b2]	Substudy A: combination RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine

Abbreviation	Term
RT-PCR	reverse transcription–polymerase chain reaction
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
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Screat	serum creatinine
Scys	serum cystatin C
SD	standard deviation
SIIV	seasonal inactivated influenza vaccine
SmPC	summary of product characteristics (European Union)
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
TBA	to be advised
T bili	total bilirubin
Th1	T-helper type 1
TOC	table of contents
UADE	unanticipated adverse device effect
UK	United Kingdom
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States package insert
VE	vaccine efficacy
VRBPAC	Center for Biologics Evaluation and Research Vaccines and Related Biological Products Advisory Committee (United States)
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WT	wild type

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