AN INTERVENTIONAL, RANDOMIZED, ACTIVE-CONTROLLED, PHASE 1/2/3 STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF BNT162b RNA-BASED VACCINE CANDIDATES IN COVID-19 VACCINE–EXPERIENCED HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted by:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	BNT162b RNA-Based COVID-19 Vaccine
US IND Numbers:	19736 and 29784
EudraCT/CTIS Number:	2022-002008-19
ClinicalTrials.gov ID:	NCT05472038
Pediatric Investigational Plan Number:	EMEA-002861-PIP02-20-M03
Protocol Number:	C4591044
Phase:	1/2/3

Brief Title:
A Study to Learn About New COVID-19 RNA Vaccine Candidates in COVID-19 Vaccine–Experienced Healthy Individuals

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Document History

Document	Version Date
Original protocol	14 June 2022
Amendment 1	27 July 2022
Amendment 2	24 August 2022
Amendment 3	14 April 2023 (protocol amendment 3 was not implemented)
Amendment 4	26 May 2023
Amendment 5	23 June 2023 (protocol amendment 5 was not implemented)
Amendment 6	27 July 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 clarification letter.

Amendment 6 (27 July 2023)

Overall Rationale for the Amendment:

Addition of BNT162b6 vaccine into Cohort 4 to describe the immune response to this new 30-µg bivalent Omicron BA.4/BA.5–modified BNT162b vaccine:

- BNT162b6 Bivalent (Original/OMI BA.4/BA.5)

given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age. Updated corresponding objectives and details in the statistical methods sections. Study intervention details and background information supporting the inclusion of this vaccine were also added.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Cover page	Added IND number 29784 and removed IND number 29525. Amended the title to remove “bivalent” and “booster.”	Per feedback from FDA/CBER, studies of BNT162b6 and BNT162b7 are to be conducted together under a new IND. Since Cohort 4 vaccine candidates include a monovalent vaccine.	Substantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
		To align with recent simplified public health vaccination schedules.	
Protocol Summary: Section 1.1, Section 1.2, and Section 1.3	Updated the text, tables, and schema with respect to the changes within Cohort 4.	To obtain data on the new 30-µg bivalent Omicron BA.4/BA.5–modified BNT162b6 vaccine in participants 18 through 55 years of age.	Substantial
Section 2 Introduction	Added text to provide background and rationale for the addition of the BNT162b6 vaccine into Cohort 4.	To obtain data on the new 30-µg bivalent BNT162b6 vaccine.	Substantial
Section 2.3.1 Risk Assessment	Updated with new information regarding myocarditis and pericarditis rates in ages 12 through 17 years and after additional doses. Applied corrections to align with the SRSD.	To align with SRSD.	Substantial
Section 1.1 Synopsis and Section 3 Objectives, Endpoints, and Estimands	Updated the text with respect to the addition of the BNT162b6 vaccine into Cohort 4.	To describe the analysis of data from Cohort 4.	Substantial
Section 4 Study Design	Updated Cohort 4–specific information in Section 4.1.	To update for the addition of the BNT162b6 vaccine into Cohort 4.	Substantial
Section 6.1 Study Interventions Administered	Updated the Cohort 4 vaccines and study intervention details.	To update for the addition of the BNT162b6 vaccine into Cohort 4.	Substantial
Section 6.3 Assignment to Study Intervention	Updated the Cohort 4 randomization scheme.	To update for the addition of the BNT162b6 vaccine into Cohort 4.	Substantial
Section 9 Statistical Considerations	Updated the analysis of data from Cohort 4.	To update for the addition of the BNT162b6 vaccine into Cohort 4.	Substantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 5.2 Exclusion Criteria	Added exclusion criterion 10 to exclude any history of myocarditis/pericarditis from Cohort 4 onwards.	Per feedback from FDA/CBER.	Substantial
Section 1.3 Schedule of Activities, Section 8.4.8 Adverse Events of Special Interest, and Section 8.10.11 Additional Procedures for Monitoring of Potential Pericarditis or Myocarditis	Updated to: - extend monitoring of cardiac symptoms through 6 weeks after study intervention administration. - amend wording for cardiologist evaluation. - classify the diagnosis of myocarditis of pericarditis as an important medical event requiring reporting as an SAE.	Per feedback from FDA/CBER.	Substantial
Section 5.2 Exclusion Criteria and Section 6.9.1 Prohibited During the Study	Updated to clarify exclusion of monoclonal antibodies.	To clarify and align with other C459 protocols based on site feedback.	Nonsubstantial
Section 8.3.4 Electronic Diary	Added text related to e-diary reminder notifications and capture of missed diary data in CRF.	To include in the protocol per FDA/CBER feedback.	Nonsubstantial
Section 8.10.1 Visit 1 - Study Intervention Administration - Day 1	Updated text related to IRT notifications.	To clarify which IRT notifications are received by blinded versus unblinded team members.	Nonsubstantial
Section 9.1.1 Estimands	Updated to remove “e-diary” when referencing reactogenicity data.	To align with data handling where reactogenicity data are compiled from the e-diary and CRF.	Nonsubstantial
Section 10.8 Appendix 8: Protocol Amendment History	Added Amendment 4 summary of changes. Clarified Amendment 3 and Amendment 5.	Protocol template requirement.	Nonsubstantial
Section 10.9 Appendix 9: Abbreviations	Updated with the BNT162b6 vaccine.	Administrative updates for the addition of the BNT162b6 vaccine to the protocol.	Nonsubstantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 11 References	Additional references for epidemiological data and new variant mutations.	To support statements made throughout the synopsis and introduction.	Nonsubstantial
All	Added reference to PSSA for reporting of safety information to Pfizer Safety and edited text in line with current process.	To capture reporting process to Pfizer Safety via PSSA.	Nonsubstantial
All	Removal of reference to "booster" in Cohort 4 and in relation to current public health vaccination schedule text.	To align with recent simplified public health vaccination schedules.	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

An Interventional, Randomized, Active-Controlled, Phase 1/2/3 Study to Investigate the Safety, Tolerability, and Immunogenicity of BNT162b RNA-Based Vaccine Candidates in COVID-19 Vaccine–Experienced Healthy Individuals

Brief Title:

A Study to Learn About New COVID-19 RNA Vaccine Candidates in COVID-19 Vaccine–Experienced Healthy Individuals

Regulatory Agency Identification Numbers:

US IND Number:	19736 and 29784
EudraCT/CTIS Number:	2022-002008-19
ClinicalTrials.gov ID:	NCT05472038
Pediatric Investigational Plan Number:	EMEA-002861-PIP02-20-M03
Protocol Number:	C4591044
Phase:	1/2/3

Rationale:

BNT162b2 (Comirnaty®) is an RNA-based vaccine that, as of April 2022, was granted full marketing authorization, conditional marketing authorization, EUA, or temporary authorization in a total of more than 140 countries for the prevention of COVID-19 caused by SARS-CoV-2. The vaccine encodes the spike protein with a modRNA, is encapsulated in RNA-LNPs, and has demonstrated potent immunogenicity, high VE, and a favorable safety profile in Phase 1, 2, and 3 human trials, as well as in real-world usage. Since the start of the pandemic, several variants have emerged, causing surges in infection rates despite uptake of vaccines. Currently, the SARS-CoV-2 Omicron variant B.1.1.529 and its sublineages are dominant globally, though the prevalence of particular sublineages continues to evolve. Within the US, in late May 2022, the BA.2 and BA.2.12.1 sublineages accounted for the majority of sequenced COVID-19 cases, and by mid-August 2022, BA.4 and BA.5 accounted for the majority. Substantial immune escape by Omicron BA.4/BA.5 from neutralizing antibodies induced by both infection and immunization has been observed, which has been attributed to the L452R and F486V spike mutations within the protein sequence of BA.4/BA.5. SARS-CoV-2 has continued to evolve with the recombinant XBB sublineages dominating within the US and globally by the end of March 2023. The XBB sublineages that have become most prevalent have a hallmark F486P mutation that confers further immune

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escape and host receptor affinity. The most current weighted estimates from the CDC for the 2-week period ending on 10 June 2023 for all sequenced cases reported for the Omicron sublineages in the US were as follows (those above 3%): XBB.1.5 (40.0%), XBB.1.16 (11.8%), XBB.1.9.1 (9.4%), XBB.2.3 (8.5%), XBB.1.16.1 (6.2%), XBB.1.9.2 (5.9%), XBB (4.8%), and EG.5 (3.7%).

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 new evolving sublineages. In light of this waning effectiveness of BNT162b2 as well as the existence of subvariants with cumulative mutations in the spike protein, development of a new vaccine that could generate an improved immune response, including against other variants, could help better protect individuals against COVID-19.

Based on this rationale, Pfizer-BioNTech will evaluate the following vaccine candidates (original protocol through protocol amendment 2):

Cohort 1: BNT162b5 Bivalent (WT/OMI BA.2), a BNT162b RNA-based vaccine consisting of a modified version of the 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.2 sublineage).

Cohorts 2 and 3: BNT162b2 Bivalent (WT/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).

Multiple real-world studies show that the bivalent (Original/OMI BA.4/BA.5) mRNA COVID-19 vaccine provides effective protection against hospitalization and additional protection among persons previously vaccinated with only WT-based mRNA vaccine(s). However, as the real-world evidence describing bivalent vaccine effectiveness continues to accumulate, several reports suggest that vaccine effectiveness against severe illness may potentially wane approximately 2 to 4 months after bivalent vaccination, though additional data continue to accumulate to better characterize the duration of protection. In light of early evidence of waning effectiveness of the bivalent (Original/OMI BA.4/BA.5) mRNA COVID-19 vaccine during periods when the subsequent Omicron sublineages were in circulation (BQ.1/BQ.1.1 and XBB/XBB.1.5), development of a more efficacious and durable vaccine that could generate an improved, longer-lasting immune response, including against current and newly emergent variants and lineages, could help better protect individuals against COVID-19.

Based on this rationale, Pfizer-BioNTech will evaluate the following vaccine candidates in protocol amendment 6:

Cohort 4: BNT162b5, BNT162b6, and BNT162b7, new BNT162b RNA-based vaccines containing different prefusion-stabilized versions of the SARS-CoV-2 spike encoded from mRNA. Bivalent and/or monovalent formulations targeting the ancestral strain of the virus

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and/or the Omicron variant (BA.4/BA.5 sublineage) will be evaluated. The Cohort 4 bivalent vaccine names use "Original" instead of "Wild Type" (or "WT"). Both terms refer to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), which is also referred to in this protocol as the reference strain.

Objectives, Endpoints, and Estimands:

Objectives	Estimands	Endpoints
Primary Safety		
Cohort 1: To describe the safety and tolerability profile of BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study 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
Cohort 2: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age, and BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study 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
Cohort 2 + Cohort 3 combined: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study 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

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Objectives	Estimands	Endpoints
Cohort 4[a]: To describe the safety and tolerability profile of BNT162b2 Bivalent 30 µg, BNT162b5 Bivalent 30 µg, BNT162b6 Bivalent 30 µg, BNT162b7 Bivalent 30 µg, and BNT162b7 Monovalent 30 µg given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study 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
Primary Immunogenicity		
Cohort 1: To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFRs from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 2/Group 4 + Cohort 3/ Group 2 combined: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to after BNT162b2 30 µg[d] given as a second booster dose to BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) to 1 month after BNT162b2, given as a second booster dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers

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Objectives	Estimands	Endpoints
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers
Cohort 2: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg[e] or 60 µg[e] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55,[e] and >55[e] years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 4[a]: To describe the immune response to BNT162b2 Bivalent 30 µg, BNT162b5 Bivalent 30 µg, BNT162b6 Bivalent 30 µg, BNT162b7 Bivalent 30 µg, and BNT162b7 Monovalent 30 µg given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers

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Objectives	Estimands	Endpoints
Secondary Immunogenicity		
Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority of the anti–reference-strain immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[d] given as a second booster dose in BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the reference-strain–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[d] given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Exploratory		
Cohort 1: To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): At baseline and 7 days, 1 month, 3 months, and 6 months after study vaccination, • GMT at each time point for each strain-specific neutralizing titer • GMFRs from before the study vaccination to each time point after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at each time point after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers

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Objectives	Estimands	Endpoints
Cohort 2/Group 1, Cohort 2/Group 2 + Cohort 3/Group 1 combined[f] Cohort 2/Group 4 + Cohort 3/Group 2 combined[f] Cohort 2/Group 3, and Cohort 2/Group 5: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg compared to BNT162b2 30 µg[f] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): At baseline and 1 month, 3 months, and 6 months after the study vaccination, • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 4[a]: To describe the immune response to BNT162b2 Bivalent 30 µg, BNT162b5 Bivalent 30 µg, BNT162b6 Bivalent 30 µg, BNT162b7 Bivalent 30 µg, and BNT162b7 Monovalent 30 µg given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): At baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination, • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each time point after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at each time point after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine group and age group.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: To describe the immune response to SARS-CoV-2 infection at the time of the COVID-19 illness visit[g] and at the convalescent visit.		• SARS-CoV-2–neutralizing titers previously specified for the respective cohorts
Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: To describe the immune response to other emerging variants (under monitoring, of interest, and/or of concern).		• SARS-CoV-2–neutralizing titers for other variants (under monitoring, of interest, and/or of concern) not already specified

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Objectives	Estimands	Endpoints
Cohort 2: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain[c] and Omicron variant in a subset of participants with PBMC samples collected.		

a. The Cohort 4 bivalent vaccines target the SARS-CoV-2 Original strain and the Omicron variant (BA.4/BA.5 sublineage). The Cohort 4 monovalent vaccine targets the Omicron variant (BA.4/BA.5 sublineage).
b. Seroresponse is defined as achieving a ≥4-fold rise from the baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
c. Reference strain is also referred to as the Original, Wild Type, or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).
d. The participants >55 years of age from C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group for this objective.
e. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from C4591031 Substudy E expanded cohort who received Bivalent BNT162b2 (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be randomly selected for this objective. The subset selected from C4591031 Substudy E will include a similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study whenever feasible.
f. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) from C4591044 Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg and from the C4591031 Substudy E expanded cohort who receive BNT162b2 30 µg as a second booster dose will be selected for this objective. The subset selected will include a similar percentage of participants with baseline positive SARS-CoV-2 infection status whenever feasible.
g. If the COVID-19 illness visit is conducted as an in-person visit, a blood sample will be taken for this assessment. No blood samples will be obtained for remote (telehealth) COVID-19 illness visits.

Overall Design:

This study is a randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new bivalent and monovalent vaccines. The study vaccine candidates are divided into cohorts, which may be studied in a staggered or parallel manner, as required by the clinical plan.

Cohort 1: Participants 18 through 55 years of age will be randomized at a ratio of 1:1 to receive a single 30-µg dose of either BNT162b5 Bivalent (WT/OMI BA.2) or BNT162b2 Bivalent (WT/OMI BA.1) as a second booster dose. Participants will be stratified by the number of months since the last dose of the COVID-19 vaccine received prior to randomization (3 to 6 months [90 to 180 days] or >6 months [>180 days]).

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Cohort 2: Participants 12 through 17 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will receive a single 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) as a second booster dose (open-label). Participants 18 through 55 years of age and >55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will be randomized 1:1 within each age group to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either 30 µg or 60 µg as a second booster dose (observer-blind).

Cohort 2: BNT162b2 Bivalent (WT/OMI BA.4/BA.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization / Blind**
1	12-17 years	3	150-365 days	30 µg	100	Open-label
2	18-55 years	3	150-365 days	30 µg	100	Randomized 1:1 Observer-blind
3	18-55 years	3	150-365 days	60 µg	100	
4	>55 years	3	150-365 days	30 µg	100	Randomized 1:1 Observer-blind
5	>55 years	3	150-365 days	60 µg	100	

Cohort 3: Participants 18 years of age and older who have received 3 prior 30-µg doses of BNT162b2, with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will receive a single 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) as a second booster dose (open-label).

Cohort 3: BNT162b2 Bivalent (WT/OMI BA.4/BA.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization / Blind**
1	18-55 years	3	150-365 days	30 µg	200	Open-label
2	>55 years	3	150-365 days	30 µg	200	Open-label

Cohort 4: Participants 18 through 55 years of age who have received 3 or 4 prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being a bivalent vaccine at least 150 days prior to Visit 1 (Day 1), will be enrolled. The Cohort 4 bivalent vaccines target the SARS-CoV-2 Original strain and the Omicron variant (BA.4/BA.5 sublineage). The Cohort 4 monovalent vaccine targets the Omicron variant (BA.4/BA.5 sublineage). Participants will be randomized at a ratio of 1:1:1:1:1 to receive a single 30-µg dose of either BNT162b2 Bivalent, BNT162b5 Bivalent, BNT162b6 Bivalent, BNT162b7 Bivalent, or BNT162b7 Monovalent (observer-blind). Participants will be stratified by the number of prior doses (3 or 4 prior doses) of a US-authorized mRNA COVID-19 vaccine received prior to randomization.

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Cohort 4: BNT162b Omicron BA.4/BA.5 Vaccine Candidates All Participants 18 Through 55 Years of Age						
Group	**Study Intervention**	**Study Dose**	**Prior Doses of mRNA COVID-19 Vaccine**	**Time Since Last Dose**	**Number of Participants**	**Randomization / Blind**
1	BNT162b2 Bivalent (Original/OMI BA.4/BA.5)	30 µg	3 or 4	≥150 days	60	Randomized 1:1:1:1:1 Observer-blind
2	BNT162b5 Bivalent (Original/OMI BA.4/BA.5)	30 µg	3 or 4	≥150 days	60	
3	BNT162b6 Bivalent (Original/OMI BA.4/BA.5)	30 µg	3 or 4	≥150 days	60	
4	BNT162b7 Bivalent (Original/OMI BA.4/BA.5)	30 µg	3 or 4	≥150 days	60	
5	BNT162b7 Monovalent (OMI BA.4/BA.5)	30 µg	3 or 4	≥150 days	60	

Number of Participants:

Cohort 1: Approximately 200 participants will be enrolled.

Cohort 2: Approximately 500 participants will be enrolled.

Cohort 3: Approximately 400 participants will be enrolled.

Cohort 4: Approximately 300 participants will be enrolled.

Study Population:

The inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

1. Ages for each cohort as follows:

   Cohort 1: Participants 18 through 55 years of age at randomization.

   Cohort 2: Participants ≥12 years of age at Visit 1.

   Cohort 3: Participants ≥18 years of age at Visit 1.

   Cohort 4: Participants 18 through 55 years of age at Visit 1.

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- Refer to the body of the protocol for reproductive criteria for male and female participants.

Participant and Disease Characteristics:

2. Participants and participants' parent(s)/legal guardian(s), as appropriate, willing and able to comply with all scheduled visits/contacts, investigational plan, laboratory tests, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if indicated), 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.

Informed Consent:

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

   The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant's legal guardian and the participant's assent, when applicable, before any study-specific activity is performed. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

Other Inclusion Criteria:

5. Cohort 1: Participants who have received 1 booster dose of a US-authorized COVID-19 vaccine, with the last prior dose being 90 or more days before Visit 1 (Day 1).

   Note: Documented confirmation of prior COVID-19 vaccines received must be obtained prior to randomization. All prior COVID-19 vaccines must be authorized for use in the US.

   Cohort 2 and Cohort 3: Participants who have received 3 prior 30-µg doses of BNT162b2, with the last dose being 150 to 365 days before Visit 1 (Day 1).

   Note: Documented confirmation of prior doses of BNT162b2 received must be obtained prior to randomization.

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Cohort 4: Participants who have received 3 or 4 prior doses of a US-authorized mRNA COVID-19 vaccine (and dose level), with the last dose being a US-authorized Omicron BA.4/BA.5–adapted bivalent vaccine and dose level at least 150 days before Visit 1 (Day 1).

Note: Documented confirmation of prior mRNA COVID-19 vaccines received must be obtained before randomization. Participants must have received mRNA COVID-19 vaccines only.

Exclusion Criteria

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

Medical Conditions:

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

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

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

4. Women who are pregnant or breastfeeding.

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

Prior/Concomitant Therapy:

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

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

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

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Prior/Concurrent Clinical Study Experience:

8. Participation in other studies involving receipt of a study intervention within 28 days before randomization. Anticipated participation in other studies involving a study intervention from randomization through the end of this study.

Other Exclusion Criteria:

9. 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.

Other Medical Conditions: From protocol amendment 6 (Cohort 4) onwards:

10. History of myocarditis or pericarditis.

Study Arms and Duration:

The study duration for each participant will be approximately 6 months. For the purposes of this protocol, study intervention refers to:

Cohort 1

- BNT162b5 Bivalent (WT/OMI BA.2) =

  BNT162b5 Wild Type and BNT162b5 OMICRON (B.1.1.529) sublineage BA.2

  (BNT162b5 RNA-LNP vaccine utilizing modRNA and encoding the P6' S)
- BNT162b2 Bivalent (WT/OMI BA.1) =

  BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.1

  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 1		
Intervention Name	BNT162b5 Bivalent (WT/OMI BA.2) (BNT162b5 Wild Type[a] and BNT162b5 OMICRON [B.1.1.529 sublineage BA.2]) Preformulated as a single vial (no dilution required)	BNT162b2 Bivalent (WT/OMI BA.1) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.1]) Preformulated as a single vial (no dilution required)
Arm Name **(group of participants receiving a specific study intervention or no study intervention)**	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Unit Dose Strength(s)	100 µg/mL	100 µg/mL

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Study Interventions – Cohort 1		
Dosage Level(s)	30 µg (15 µg BNT162b5 Wild Type and 15 µg BNT162b5 OMICRON [B.1.1.529 sublineage BA.2])	30 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.1])
Route of Administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental and active comparator
IMP or NIMP/AxMP	IMP	IMP

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

Study Arms – Cohort 1		
Arm Title	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Arm Type	Experimental	Experimental and active comparator
Arm Description	Participants will receive 30 µg of BNT162b5 Bivalent (WT/OMI BA.2) at Visit 1.	Participants will receive 30 µg of BNT162b2 Bivalent (WT/OMI BA.1) at Visit 1.

Cohort 2

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) =
  BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 2	
Intervention Name	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated as a single vial (no dilution required)
Arm Name (group of participants receiving a specific study intervention or no study intervention)	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg or 60 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) (30 µg BNT162b2 Wild Type and 30 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP/AxMP	IMP

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

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Study Arms – Cohort 2					
Arm Title	Group 1: 12-17 years, 30 µg	Group 2: 18-55 years, 30 µg	Group 3: 18-55 years, 60 µg	Group 4: >55 years, 30 µg	Group 5: >55 years, 60 µg
Arm Type	Experimental	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg

Cohort 3

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) =
  BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 3	
Intervention Name	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated as a single vial (no dilution required)
Arm Name **(group of participants receiving a specific study intervention or no study intervention)**	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP/AxMP	IMP

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

Study Arms – Cohort 3		
Arm Title	Group 1: 18-55 years, 30 µg	Group 2: >55 years, 30 µg
Arm Type	Experimental	Experimental
Arm Description	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1

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Cohort 4

The Cohort 4 bivalent vaccine names use "Original" instead of "Wild Type" (or "WT"). Both terms refer to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), which is also referred to in this protocol as the reference strain. Study intervention labeling may contain "Wild Type/WT" or "Original" interchangeably.

- BNT162b2 Bivalent (Original/OMI BA.4/BA.5) =
  BNT162b2 Original and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)
- BNT162b5 Bivalent (Original/OMI BA.4/BA.5) =
  BNT162b5 Original and BNT162b5 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b5 RNA-LNP vaccine utilizing modRNA and encoding the P6' S)
- BNT162b6 Bivalent (Original/OMI BA.4/BA.5) =
  BNT162b6 Original and BNT162b6 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b6 RNA-LNP vaccine utilizing modRNA for the P6 S)
- BNT162b7 Bivalent (Original/OMI BA.4/BA.5) =
  BNT162b7 Original and BNT162b7 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b7 RNA-LNP vaccine utilizing modRNA for the P6 S)
- BNT162b7 Monovalent (OMI BA.4/BA.5) =
  BNT162b7 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b7 RNA-LNP vaccine utilizing modRNA for the P6 S)

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Study Interventions – Cohort 4					
Intervention Name	BNT162b2 Bivalent (Original/OMI BA.4/BA.5) (BNT162b2 Original[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated in a single vial (no dilution required)	BNT162b5 Bivalent (Original/OMI BA.4/BA.5) (BNT162b5 Original[a] and BNT162b5 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated in a single vial (no dilution required)	BNT162b6 Bivalent (Original/OMI BA.4/BA.5) (BNT162b6 Original[a] and BNT162b6 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated in a single vial (no dilution required)	BNT162b7 Bivalent (Original/OMI BA.4/BA.5) (BNT162b7 Original[a] and BNT162b7 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated in a single vial (no dilution required)	BNT162b7 Monovalent (OMI BA.4/BA.5) (BNT162b7 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated in a single vial (no dilution required)
Arm Name (group of participants receiving a specific study intervention or no study intervention)	BNT162b2 Bivalent (Original/OMI BA.4/BA.5)	BNT162b5 Bivalent (Original/OMI BA.4/BA.5)	BNT162b6 Bivalent (Original/OMI BA.4/BA.5)	BNT162b7 Bivalent (Original/OMI BA.4/BA.5)	BNT162b7 Monovalent (OMI BA.4/BA.5)
Unit Dose Strength(s)	100 µg/mL	100 µg/mL	100 µg/mL	100 µg/mL	100 µg/mL
Dosage Level(s)	30 µg (15 µg BNT162b2 Original and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	30 µg (15 µg BNT162b5 Original and 15 µg BNT162b5 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	30 µg (15 µg BNT162b6 Original and 15 µg BNT162b6 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	30 µg (15 µg BNT162b7 Original and 15 µg BNT162b7 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	30 µg (30 µg BNT162b7 OMICRON [B.1.1.529 sublineage BA.4/BA.5])
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Active comparator	Experimental	Experimental	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP	IMP

a. Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as Wild Type, WT, and the reference strain. Study intervention vial labels for the Cohort 4 bivalent vaccines may specify WT instead of Original.

Study Arms – Cohort 4					
Arm Title	BNT162b2 Bivalent (Original/OMI BA.4/BA.5)	BNT162b5 Bivalent (Original/OMI BA.4/BA.5)	BNT162b6 Bivalent (Original/OMI BA.4/BA.5)	BNT162b7 Bivalent (Original/OMI BA.4/BA.5)	BNT162b7 Monovalent (OMI BA.4/BA.5)
Arm Type	Active comparator	Experimental	Experimental	Experimental	Experimental

Statistical Methods:

Cohorts 1, 2, and 4:

For the objectives evaluated separately within Cohort 1, Cohort 2, and Cohort 4, the sample size is not based on any statistical hypothesis testing since all objectives are descriptive. The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each vaccine group. The primary immunogenicity objectives will be evaluated descriptively by GMT, GMFR, and percentage of participants with seroresponse of SARS-CoV-2–neutralizing titers at the various time points.

Cohort 2 + Cohort 3 combined:

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

For the >55-year age group, the primary immunogenicity objective will be evaluated by GMR of the Omicron BA.4/BA.5–neutralizing titers and difference in percentage of participants with seroresponse to the Omicron BA.4/BA.5 strain induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) relative to BNT162b2 at 1 month after the study vaccination. The BNT162b2 group is a historic comparator, from approximately 300 participants >55 years of age who received BNT162b2 30 µg as a fourth dose in C4591031 Substudy E expanded cohort, after 3 prior 30-µg doses of BNT162b2. Assuming a 20% nonevaluable rate, with approximately 300 participants to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) in this study and approximately 300 participants who received BNT162b2 from C4591031 Substudy E, there will be approximately 480 evaluable participants (240 BNT162b2 Bivalent [WT/OMI BA.4/BA.5] and 240 BNT162b2) contributing to the immunogenicity evaluation. Superiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 1; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

For the 18- through 55-year age group, the primary immunogenicity objective will be evaluated by GMR of the Omicron BA.4/BA.5–neutralizing titers and difference in percentage of participants with seroresponse to the Omicron BA.4/BA.5 strain induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) relative to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) in the >55-year age group at 1 month after the study vaccination. Assuming a 20% nonevaluable rate, with approximately 300 participants to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) in each age group, there will be approximately 480 evaluable participants (240 in the 18- through 55-year age group and 240 in the >55-year age group) contributing to the immunogenicity evaluation. Noninferiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

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The secondary immunogenicity objective for the >55-year age group will be evaluated by GMR of the reference-strain–neutralizing titers induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) relative to BNT162b2 (historic comparator) at 1 month after the study vaccination. Noninferiority based on the GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8.

The primary objective for the >55-year age group will be evaluated first, followed by the secondary objective for GMR in the >55-year age group and then the primary objective for the 18-through 55-year age group. Each of these objectives will be evaluated only if the previous objective is met. Each primary objective involves 2 hypotheses: GMR and seroresponse rate difference. Both hypotheses within the objective must be established before evaluating the next objective in the sequence. Therefore, the overall type I error is fully controlled.

The other secondary immunogenicity objectives will be evaluated descriptively by GMT, GMFR, the difference in percentages of participants with seroresponse, and the associated 95% CIs for SARS-CoV-2–neutralizing titers at the various time points.

Ethical Considerations:

The available safety and immunogenicity data from ongoing Pfizer-BioNTech clinical trials and real-world effectiveness and safety data, combined with available nonclinical data with BNT162b vaccines and data from nonclinical and clinical trials with the same or related RNA components or antigens, support a favorable benefit/risk profile and support clinical development of BNT162b2, BNT162b5, BNT162b6, and BNT162b7 bivalent vaccines, and of BNT162b7 monovalent vaccine. Taking into account the measures to minimize risk to study participants, the potential risks identified in association with the study intervention are justified by the anticipated benefits that may be afforded to healthy participants.

- As all vaccines under study use the same modRNA platform and LNP formulation as BNT162b2, their safety profiles are expected to be similar to that of BNT162b2. Based on the experience with BNT162b2, the potential risks for BNT162b2 include the following:
    - Local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fever, fatigue, headache, chills, muscle pain, and joint pain.
    - Very rare cases of myocarditis and pericarditis have been reported after authorization in recipients of BNT162b2.
    - Cases of anaphylaxis have been reported; however, the frequency is not estimable from the available data.

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- The study procedure–related risks include:
  - *Original protocol and amendments 1 and 2:* Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.
  - Venipuncture will be performed during the study.
- Participants will be expected to commit time and may experience some discomfort while undergoing study assessments.

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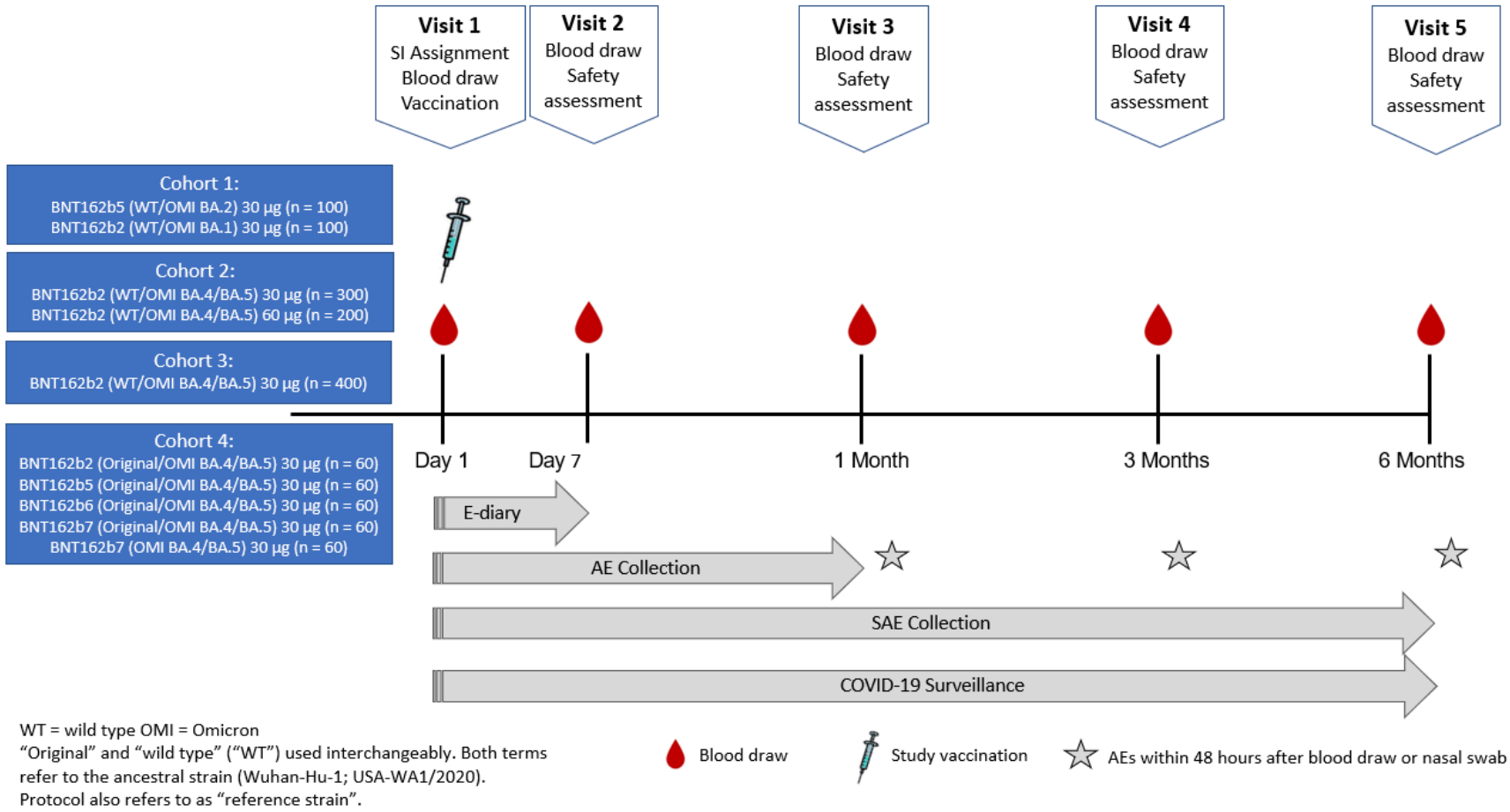
1.2. Schema



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1.3. Schedule of Activities

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

An unplanned potential COVID-19/MIS-C illness visit and unplanned potential COVID-19/MIS-C convalescent visit are required at any time between Visit 1 (vaccination) and Visit 5 (6-month follow-up visit) that COVID-19 symptoms are reported. During the 7 days following each dose, potential COVID-19/MIS-C symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19/MIS-C illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19/MIS-C illness rather than vaccine reactogenicity. For details, see Section 8.10.7.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant. Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, study visits, blood sample collection/analysis, or other procedures may be halted or discontinued.

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								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Obtain informed consent and assent (if appropriate)	X							If vaccination is temporarily delayed, per Section 5.5, consent need not be obtained again on the day of vaccination.
Assign participant number	X							If participant is from a prior Pfizer COVID-19 study, record the participant number of the prior study in the CRF. If more than 1 study, record the participant number of both the most recent prior study and the first study.
Obtain demography and medical history data (including confirmed COVID-19 diagnosis or asymptomatic positive SARS-CoV-2 test result)	X							
Obtain documentation of all prior COVID-19 vaccines	X							Record details in the prior COVID-19 vaccination CRF.
Urine pregnancy test (if appropriate)	X							Refer to Section 8.3.5.
Confirm use of contraceptives (if appropriate)	X	X	X					Refer to Section 5.3.1.

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								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Measure height and weight	X							
Perform clinical assessment	X	X	X	X	X			Including, if indicated, a physical examination (Section 8.3.1).
Record nonstudy vaccine information	X	X	X	X	X			Refer to Section 6.9.
Record prohibited medication use		X	X	X	X	X	X	Refer to Section 6.9.1.
Confirm eligibility	X							
Measure body temperature	X							
Review temporary delay criteria	X							
Nasal (midturbinate) swab for SARS-CoV-2 NAAT	X					X		

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								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Blood sample for immunogenicity assessment	~50 mL / 10 mL	~20 mL / 10 mL	~50 mL / 10 mL	~20 mL / 10 mL	~20 mL / 10 mL	~20 mL / 10 mL*	~20 mL / 10 mL	50 mL/20 mL is to be collected from participants ≥18 years of age; 10 mL is to be collected from participants 12 through 17 years of age. *If the Potential COVID-19 Illness Visit is an in-person visit, a blood sample will be taken. Blood sample collection may be halted or discontinued upon notification by Pfizer.
Blood sample for PBMC isolation	~130 mL	~130 mL	~130 mL	~130 mL	~130 mL			Applicable at designated sites only with optional consent given by participants ≥18 years of age. See Section 8.2.2. Not applicable to Cohort 1, Cohort 3, or Cohort 4.

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								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Blood sample for HLA typing	~5 mL							Applicable at designated sites only with optional consent given by participants ≥18 years of age. See Section 8.2.2. Not applicable to Cohort 1, Cohort 3, or Cohort 4.
Obtain randomization number using the IRT system	X							
Obtain the participant's vaccine vial allocation using the IRT system	X							
Administer study intervention	X							Refer to Section 6.1.1
Assess acute reactions for at least 30 minutes after study intervention administration	X							
Explain participant communication methods (including for COVID-19 illness and reactogenicity e-diary completion and severe reactogenicity symptoms), assist the participant or participant's parent(s)/legal guardian with downloading the app or issue provisioned device, if required	X							

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								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Provide thermometer and measuring device	X							
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection (or collection by parent/legal guardian) of nasal swabs	X	X	X	X				
Ask/remind the participant or participant's parent(s)/legal guardian to contact the site if participant experiences any severe (Grade 3) reactogenicity symptoms	X	X						
Ask/remind the participant or participant's parent(s)/legal guardian to contact the site if a medically attended event or hospitalization occurs	X	X	X	X				
Ask/remind the participant or participant's parent(s)/legal guardian to contact site immediately if participant experiences any symptoms as detailed in Section 8.10.7 (COVID-19/MIS-C surveillance)	X	X	X	X				
Participant completes COVID-19 illness e-diary	←	—	—	—	→			Refer to Section 8.2 and Section 8.10.7.

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								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Ask/remind the participant or participant's parent(s)/legal guardian to contact site immediately if participant experiences any symptoms of acute chest pain, shortness of breath, or palpitations	X	X	X*					Refer to Section 8.10.11. *From Cohort 4 onwards, symptoms reported through 6 weeks after study intervention.
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄	►						If Visit 2 occurs on Day 6, continue to review e-diary data through Day 7.
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	Includes nonserious AEs through Visit 3, any AEs occurring up to 48 hours after a blood draw or nasal swab collection, and SAEs through the end of study (see Section 8.4.1).

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								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)						X	X	
Assist the participant or participant's parent(s)/legal guardian to delete the e-diary application or collect the provisioned device					X			

Abbreviations: CRF = case report form; HLA = human leukocyte antigen; IRT = interactive response technology; MIS-C = multisystem inflammatory syndrome in children; NAAT = nucleic acid amplification test; PBMC = peripheral blood mononuclear cell; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

2. INTRODUCTION

BNT162b2 (Comirnaty) is an RNA-based vaccine that, as of April 2022, was granted full marketing authorization, conditional marketing authorization, EUA, or temporary authorization in a total of more than 140 countries for the prevention of COVID-19 caused by SARS-CoV-2.[1] In the US, it has been fully licensed for use in individuals 16 years of age and above as of 23 August 2021.[2] A third dose of BNT162b2 has been granted EUA in the US and many other countries to reduce the risk of infection in light of emerging new SARS-CoV-2 variants and increasing incidence of COVID-19 disease.[3,4,5] In the US, a fourth dose was granted EUA for individuals 50 years of age and older as well as for individuals 12 years of age and older with certain kinds of immunocompromising conditions.[6] The bivalent vaccine BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) was first authorized for emergency use in the US on 31 August 2022 for individuals 12 years of age and older as a single booster dose after either completion of primary vaccination or after the most recent booster dose with an authorized or approved monovalent COVID-19 vaccine.[7] Finally, as of 18 April 2023, US FDA reissued the EUA for the current bivalent mRNA COVID-19 vaccines to be used for all doses administered to individuals 6 months of age and older.[8]

All versions of the vaccine encode the spike protein(s) with a modRNA, encapsulated in RNA-LNPs, which has demonstrated potent immunogenicity, high VE, and a favorable safety profile in Phase 1, 2, and 3 human trials,[9] as well as in real-world usage.[10] As SARS-CoV-2 continues to circulate at very high levels,[11] Pfizer/BioNTech are investigating next-generation, RNA-based COVID-19 vaccines, including BNT162b5, BNT162b6 and BNT162b7 bivalent and BNT162b7 monovalent vaccines, to further protect against COVID-19 caused by other emergent and potentially more antigenically diverse variants.

2.1. Study Rationale

Since the start of the pandemic, several variants have emerged, causing surges in infection rates, despite uptake of vaccines. Currently, the SARS-CoV-2 Omicron variant B.1.1.529 remains dominant in many countries though the prevalence of its sublineages has rapidly changed in recent months.[11,12] Within the US, in late May 2022, the BA.2 and BA.2.12.1 sublineages accounted for the majority of sequenced COVID-19 cases, by mid-August 2022, BA.4 and BA.5 accounted for the majority, and by the end of January 2023, the XBB sublineages accounted for the majority.[13] The most current weighted estimates from the CDC for the 2-week period ending on 10 June 2023 for all sequenced cases reported for the Omicron sublineages in the US were as follows (those above 3%): XBB.1.5 (40%), XBB.1.16 (11.8%), XBB.1.9.1 (9.4%),, XBB.2.3 (8.5%), XBB.1.16.1 (6.2%), XBB.1.9.2 (5.9%), XBB (4.8%), and EG.5 (3.7%).[14]

The UK Health Security Agency reports that the effectiveness of ChAdOx1-S, BNT162b2, and mRNA-1273 (pooled analysis) against hospitalization is 88% (range, 78%-93%) for the Omicron variant 2 or more weeks after a booster dose.[15] However, other studies have demonstrated that the effectiveness of BNT162b2 against SARS-CoV-2 infection and COVID-19 disease wanes over a period of months, particularly in the context of

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variants.[16,17,18] In light of this waning effectiveness of the primary 2-dose 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 the Omicron variant, development of new vaccine that could generate an improved immune response, including against other variants, could help better protect individuals against COVID-19.

Based on this rationale, Pfizer-BioNTech will evaluate the following vaccine candidates:

Original protocol (Cohort 1): BNT162b5 Bivalent (WT/OMI BA.2) consists of BNT162b5 Wild Type (ancestral strain, Wuhan-Hu-1; USA-WA1/2020) combined with BNT162b5 OMICRON (BA.2 sublineage), which has been designed to produce an improved antibody response against SARS-CoV-2. BNT162b5 Bivalent (WT/OMI BA.2) uses the same modRNA platform, manufacturing processes, and LNP formulation as BNT162b2. Its active substance is a modified version of the mRNA segment used in BNT162b2 encoding the spike protein of SARS-CoV-2.

Protocol amendments 1 and 2 (Cohorts 2 and 3): Because of the emergence of other Omicron sublineages, such as Omicron BA.4 and BA.5, which alone account for 5.3% (BA.4) and 88.8% (BA.5) of sequenced COVID-19 cases as of the week ending 13 August 2022,[13] and in line with a request by the FDA to begin clinical trials with modified vaccines containing an Omicron BA.4/BA.5 component,[19] a second cohort of approximately 500 participants has been added to the study in protocol amendment 1 to evaluate BNT162b2 Bivalent (WT/OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants ≥12 years of age. Cohort 2 will also investigate a higher dose (60 µg) of BNT162b2 (WT/OMI BA.4/BA.5) in participants ≥18 years of age. A third cohort of approximately 400 participants has been added to the study in protocol amendment 2 in order to have sufficient power to evaluate BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster dose in BNT162b2-experienced participants ≥18 years of age. BNT162b2 Bivalent (WT/OMI BA.4/BA.5) consists 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).

Multiple real-world studies show that the bivalent (Original/OMI BA.4/BA.5) mRNA COVID-19 vaccine provides effective protection against hospitalization and additional protection among persons previously vaccinated with only WT-based mRNA vaccine(s). Reported absolute vaccine effectiveness against hospitalization (reference group: unvaccinated) has ranged from 59% (95% CI: 44, 70) among immunocompetent adults ≥18 years of age[20] to 84% (95% CI: 64, 93) among immunocompetent adults ≥65 years of age.[21] Reported relative vaccine effectiveness against severe illness (reference group: only ≥2 WT-based mRNA doses) has ranged from approximately 40% to 80%, with estimates varying depending on factors such as age, time since last WT-based dose, and time elapsed since a prior SARS-CoV-2 infection.[22,23,24] However, as the real-world evidence describing bivalent vaccine effectiveness continues to accumulate, several reports suggest that vaccine effectiveness against severe illness may potentially wane approximately 2 to 4 months after bivalent vaccination,[23,24,25] though additional data continue to accumulate to better

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characterize duration of protection. In light of early evidence of waning effectiveness of the bivalent (Original/OMI BA.4/BA.5) mRNA COVID-19 vaccine during periods when the subsequent Omicron sublineages were in circulation (BQ.1/BQ.1.1 and XBB/XBB.1.5), development of a more efficacious and durable vaccine that could generate an improved, longer-lasting immune response, including against current and newly emergent variants and lineages, could help better protect individuals against COVID-19.

Protocol amendment 6 (Cohort 4): Based on the above rationale, Pfizer-BioNTech will now evaluate new BNT162b bivalent and/or monovalent vaccines (BNT162b5, BNT162b6, and BNT162b7) containing different prefusion-stabilized versions of the SARS-CoV-2 spike encoded from mRNA. These vaccines use the same modRNA platform, manufacturing processes, and LNP formulation as BNT162b2. The modifications of the mRNA segment(s) are intended to expose a broader array of neutralizing epitopes in the spike protein(s), hence potentially improving the immunogenic response. The modifications for a specific vaccine design (BNT162b5, BNT162b6, BNT162b7) are consistent, irrespective of vaccine valency and strain background. Specifically, the following vaccine candidates will be evaluated in Cohort 4: BNT162b5 Bivalent (Original/OMI BA.4/BA.5), BNT162b6 Bivalent (Original/OMI BA.4/BA.5), and BNT162b7 Bivalent (Original/OMI BA.4/BA.5). In addition, BNT162b7 Monovalent (OMI BA.4/BA.5) will be evaluated. BNT162b2 Bivalent (Original/OMI BA.4/BA.5) will be included as comparator.

2.2. Background

SARS-CoV-2, a novel β-coronavirus, is a highly transmissible and pathogenic respiratory virus responsible for the ongoing COVID-19 pandemic. Studies of SARS-CoV-2 and SARS-CoV, a closely related coronavirus that caused the 2003 SARS pandemic, demonstrated that effective antibody protection could be achieved through spike protein–specific antibodies.[26,27] 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 due to 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.[17] In another large study conducted in approximately 2.5 million UK adults vaccinated with either ChAdOx1, 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.[18]

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A recent 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 wild-type 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.[28] Moreover, the Omicron sublineages BA.4 and BA.5 have demonstrated substantial immune escape from neutralizing antibodies induced by both infection and immunization,[29] which has been attributed to the L452R and F486V spike mutations within the protein sequence of BA.4 and BA.5.[30] SARS-CoV-2 has continued to evolve with the recombinant XBB sublineages dominating within the US and globally by the end of March 2023.[12,13] The XBB sublineages that have become most prevalent have a hallmark F486P mutation that confers further immune escape and host receptor affinity.[13,31,32]

BNT162b5, BNT162b6, and BNT162b7 contain stabilized versions of the original SARS-CoV-2 spike protein mRNA that improve upon the BNT162b2 design in further constraining the spike in a prefusion conformation and the RBD in a state that may be more favorable to the presentation of broadly neutralizing epitopes. The designs of BNT162b5, BNT162b6, and BNT162b7 differ from that of BNT162b2 in the addition of proline substitutions to further stabilize the prefusion conformation. BNT162b6 and BNT162b7 additionally differ from BNT162b5 at 2 of those proline substitutions as well as in the addition of cysteine residues to form an interprotomer disulfide bridge. BNT162b6 and BNT162b7 also differ from one another at the location of their cysteine mutations, resulting in differences in the location and distance of the disulfide bridges and consequent constraint of the RBD positioning. Nonclinical studies show that these designs increase prefusion spike thermostability and improve immunogenicity compared to BNT162b2 when administered as a booster dose or primary series in mice.

A recommendation issued by the FDA on 30 June 2022 described the need to modify existing vaccines to address circulating variants and requested manufacturers to begin clinical trials with modified vaccines containing an Omicron BA.4/BA.5 component.[19] The additional studies to evaluate BNT162b vaccines, targeting emerging Omicron sublineages and other variants, may further inform decision-making for future vaccinations as the pandemic further evolves.

2.2.1. Clinical Overview

Study C4591001 (NCT04368728) is a 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.[33] 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

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(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.[34]

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.[35] 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 is prevalent.

Safety data from approximately 38,000 participants at least 16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose demonstrated a favorable safety profile. Available safety data from all participants enrolled through the 14 November 2020 data cutoff (N = 43,252), which includes late enrollment of additional adolescent and adult participants, were consistent with the safety profile for the approximately 38,000 participants with a median follow-up of 2 months and also did not raise specific safety concerns.[34]

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

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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.[9]

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.[36] 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.[37]

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.[3] 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.[4,5]

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.[38]

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, in participants 18 through 55 years of age, the monovalent Omicron-modified vaccine (at a 30-µg dose level) showed a similar local and systemic reactogenicity event profile as the prototype BNT162b2 vaccine at the

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same dose level. In participants >55 years of age, monovalent and bivalent Omicron-modified vaccines at the 30-µg dose level showed a similar local and systemic reactogenicity event profile as the prototype BNT162b2 vaccine. In the older age group at the 60-µg dose level, mild to moderate injection site pain, fatigue, and muscle pain were more common compared to the 30-µg dose level. In participants >55 years of age, without evidence of COVID-19 infection, Omicron BA.1 neutralization activity substantially increased with an Omicron-modified monovalent or bivalent vaccine as a fourth dose. Moreover, the Omicron-modified variant vaccines as a fourth dose elicit improved Omicron response against the Omicron BA.4/BA.5 sublineages, albeit at a lower level compared to the response against Omicron BA.1.[39]

Original protocol, protocol amendments 1 and 2: BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and BNT162b5 Bivalent (WT/OMI BA.2) have not been administered to humans before; however, they are highly similar to the combination vaccine under evaluation in C4591031 Substudy E.

Protocol amendment 6: Since the prevalence of Omicron sublineages remains high following the EUA of BNT162b2 Bivalent (Original/OMI BA.4/BA.5), this study will now evaluate additional new bivalent vaccines targeting the ancestral strain and Omicron BA.4/BA.5 and a new monovalent vaccine targeting Omicron BA.4/BA.5 alone.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with several SARS-CoV-2 vaccines now in use under marketing authorizations or EUAs. The available safety and immunogenicity data from ongoing Pfizer-BioNTech clinical trials and real-world effectiveness and safety data, combined with available nonclinical data with BNT162 vaccines and data from nonclinical and clinical trials with the same or related RNA components or antigens, support a favorable benefit/risk profile and support continued clinical development of BNT162b2, BNT162b5, BNT162b6, and BNT162b7 bivalent and monovalent vaccines.

Continued clinical investigation is justified, given:

- The threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection.
- The threat posed by the SARS-CoV-2 variants emerging worldwide.
- The potential need for enhancing immune responses to overcome waning immunity.
- The likelihood that COVID-19 will become endemic and a seasonal burden like other respiratory pathogens.[40,41]

More detailed information about the known and expected benefits and risks and reasonably expected AEs of the study interventions may be found in the IB, which is the SRSD for this study.

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2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Interventions: BNT162b2 Bivalent, BNT162b5 Bivalent, BNT162b6 Bivalent, BNT162b7 Bivalent, and BNT162b7 Monovalent RNA-Based COVID-19 Vaccine Candidates		
For BNT162b2: Pfizer has identified the most common risks for BNT162b2 as local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fever, fatigue, headache, chills, muscle pain, and joint pain. Other risks identified by Pfizer for BNT162b2 are lymphadenopathy; hypersensitivity reactions, such as rash, pruritus, urticaria, angioedema, and anaphylaxis; and myocarditis and pericarditis. The identified adverse reactions in local product labels may vary depending on the requirements of the respective regulatory authorities (eg, EU-SmPC and USPI). For BNT162b2 Omicron-modified vaccines, BNT162b2 OMICRON (BA.1 sublineage) and 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; and the safety profile has been similar to that of BNT162b2. For BNT162b5 and BNT162b6 bivalent and BNT162b7 monovalent and bivalent vaccines: These vaccines have the same modRNA platform (with sequence changes intended to improve the	These are common adverse reactions seen with other vaccines as well as the COVID-19 vaccine. Data available from the C4591001 study showed low incidence of severe or serious events and no clinically concerning safety observations across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status.[34] Data available from the C4591031 Substudy E showed that mild to moderate injection site pain, fatigue, and muscle pain were more common following a 60-µg dose compared to a 30-µg dose. 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. Based on accumulating data, the reporting rates of myocarditis and pericarditis after primary series in children ages 5 to <12 years are lower than in ages 12 through 17 years. Rates of myocarditis and pericarditis after additional doses do not appear to be higher	Local reactions and systemic events will be recorded using a reactogenicity e-diary to monitor local reactions and systemic events in real time. Collection of AEs from signing of the ICD through 1 month and SAEs through 6 months after study vaccination. DMC review throughout the study to review all safety data. Specific reference to identified risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.10.11.

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Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
immune response [BNT162b5, BNT162b6, BNT162b7] and that are Omicron-specific [BNT162b5 OMICRON (BA.2 sublineage), BNT162b5 OMICRON (BA.4/BA.5 sublineage), BNT162b6 OMICRON (BA.4/BA.5 sublineage), and BNT162b7 OMICRON (BA.4/BA.5 sublineage)]) and LNP formulations as BNT162b2; and the safety profile has not been found to be different from that of BNT162b2.	than after the second dose. 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 previous studies and has resulted in identification of some additional adverse reactions (risks) as noted in the SRSD.	
Study Procedures		
Original protocol and amendments 1 and 2: Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Monitoring for cases of COVID-19 developing during the study as part of the COVID-19 surveillance.
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 the study may be:

- Receipt of a further dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey better protection against the SARS-CoV-2 wild-type (ancestral) strain and/or variants [*original protocol and amendments 1 and 2:* during a global pandemic].

- Contributing to research to help others [*original protocol and amendments 1 and 2:* in a time of global pandemic].

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants as stated in Section 2.3.1, the potential risks identified in association with BNT162b RNA-based COVID-19 vaccines are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Refer to Table 1, Table 3, and Table 4 for details of the Cohort 2 group, Cohort 3 group, and Cohort 4 group, respectively.

Objectives	Estimands	Endpoints
Primary Safety		
Cohort 1: To describe the safety and tolerability profile of BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study 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

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Objectives	Estimands	Endpoints
Cohort 2: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age, and BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study 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
Cohort 2 + Cohort 3 combined: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study 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
Cohort 4[a]: To describe the safety and tolerability profile of BNT162b2 Bivalent 30 µg, BNT162b5 Bivalent 30 µg, BNT162b6 Bivalent 30 µg, BNT162b7 Bivalent 30 µg, and BNT162b7 Monovalent 30 µg given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study 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

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Objectives	Estimands	Endpoints
Primary Immunogenicity		
Cohort 1: To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 2/Group 4 + Cohort 3/ Group 2 combined: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to after BNT162b2 30 µg[d] given as a second booster dose to BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) to 1 month after BNT162b2, given as a second booster dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers

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Objectives	Estimands	Endpoints
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers
Cohort 2: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg[e] or 60 µg[e] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55,[e] and >55[e] years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 4[a]: To describe the immune response to BNT162b2 Bivalent 30 µg, BNT162b5 Bivalent 30 µg, BNT162b6 Bivalent 30 µg, BNT162b7 Bivalent 30 µg, and BNT162b7 Monovalent 30 µg given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers

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Objectives	Estimands	Endpoints
Secondary Immunogenicity		
Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority of the anti–reference-strain immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[d] given as a second booster dose in BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the reference-strain–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 2/Group 2 + Cohort 3/Group 1 combined[f] and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[d] given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Exploratory		
Cohort 1: To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): At baseline and 7 days, 1 month, 3 months, and 6 months after study vaccination, • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to 7 days after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 7 days after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers

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Objectives	Estimands	Endpoints
Cohort 2/Group 1, Cohort 2/Group 2 + Cohort 3/Group 1 combined,[f] Cohort 2/Group 4 + Cohort 3/Group 2 combined,[f] Cohort 2/Group 3, and Cohort 2/Group 5: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg compared to BNT162b2 30 µg[f] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): At baseline and 1 month, 3 months, and 6 months after study vaccination, • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 4[a]: To describe the immune response to BNT162b2 Bivalent 30 µg, BNT162b5 Bivalent 30 µg, BNT162b6 Bivalent 30 µg, BNT162b7 Bivalent 30 µg, and BNT162b7 Monovalent 30 µg given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): At baseline and 7 days, 1 month, 3 months, and 6 months after study vaccination, • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each time point after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at each time point after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: To describe the immune response to SARS-CoV-2 infection at the time of the COVID-19 illness visit[g] and at the convalescent visit.		• SARS-CoV-2–neutralizing titers previously specified for the respective cohorts
Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: To describe the immune response to other emerging variants (under monitoring, of interest, and/or of concern).		• SARS-CoV-2–neutralizing titers for other variants (under monitoring, of interest, and/or of concern) not already specified

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Objectives	Estimands	Endpoints
Cohort 2: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain[c] and Omicron in a subset of participants with PBMC samples collected.		

a. The Cohort 4 bivalent vaccines target the SARS-CoV-2 Original strain and the Omicron variant (BA.4/BA.5 sublineage). The Cohort 4 monovalent vaccine targets the Omicron variant (BA.4/BA.5 sublineage).
b. Seroresponse is defined as achieving a ≥4-fold rise from the baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
c. Reference strain is also referred to as the Original, Wild Type, or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).
d. The participants >55 years of age from C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group for this objective.
e. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from C4591031 Substudy E expanded cohort who received BNT162b2 Bivalent (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be selected for this objective. The subset selected from C4591031 Substudy E will include similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study whenever feasible.
f. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) from C4591044 Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg and from the C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be selected for this objective. The subset selected will include a similar percentage of participants with baseline positive SARS-CoV-2 infection status whenever feasible.
g. If the COVID-19 illness visit is conducted as an in-person visit, a blood sample will be taken for this assessment. No blood samples will be obtained for remote (telehealth) COVID-19 illness visits.

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new bivalent and monovalent vaccines. The study duration for each participant will be approximately 6 months. The study vaccine candidates are divided into cohorts, which may be studied in a staggered or parallel manner, as required by the clinical plan.

Refer to the schema in Section 1.2.

Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, subsequent collection of blood samples from participants in that group may be halted and/or not analyzed and study visits or other procedures may be discontinued.

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An EDMC will review cumulative unblinded data throughout the study. Refer to Appendix 1, Section 10.1.5.1.

Cohort 1 Design

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

- BNT162b5 Bivalent (WT/OMI BA.2) 30 µg
- BNT162b2 Bivalent (WT/OMI BA.1) 30 µg

Participants 18 through 55 years of age will be randomized at a ratio of 1:1 to receive a single 30-µg dose of 1 of the 2 study interventions as a second booster dose. Participants will be stratified by the number of months since the last dose of COVID-19 vaccine received prior to randomization (3 to 6 months [90 to 180 days] or >6 months [>180 days]). Approximately 200 participants will be enrolled in this cohort.

Cohort 2 Design

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

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg
- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg

Participants 12 through 17 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will receive a single 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) as a second booster dose (open-label). Participants 18 through 55 and >55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will be randomized 1:1 within each age group to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either 30 µg or 60 µg as a second booster dose (observer-blind). Approximately 500 participants will be enrolled into this cohort per Table 1.

Table 1. Cohort 2 Design

Cohort 2: BNT162b2 Bivalent (WT/OMI BA.4/BA.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization / Blind**
1	12-17 years	3	150-365 days	30 µg	100	Open-label
2	18-55 years	3	150-365 days	30 µg	100	Randomized 1:1 Observer-blind
3	18-55 years	3	150-365 days	60 µg	100	
4	>55 years	3	150-365 days	30 µg	100	Randomized 1:1 Observer-blind
5	>55 years	3	150-365 days	60 µg	100	

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To evaluate the immunogenicity objective for Cohort 2, a subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from the C4591031 Substudy E expanded cohort who received Bivalent BNT162b2 (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be selected as the control group for the descriptive immunogenicity summary (Table 2). The subset selected from C4591031 Substudy E will include similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study whenever feasible.

Table 2. Cohort 2 Immunogenicity Control Groups From C4591031 Substudy E

C4591031 Substudy E Subset			
Participant Age Group	**Vaccine Group**	**Dose**	**Number of Participants**
18-55 years	Bivalent BNT162b2 (WT/OMI BA.1)	30 µg	100
18-55 years	Bivalent BNT162b2 (WT/OMI BA.1)	60 µg	100
>55 years	Bivalent BNT162b2 (WT/OMI BA.1)	30 µg	100
>55 years	Bivalent BNT162b2 (WT/OMI BA.1)	60 µg	100

Note: Vaccine group name in C4591031 Substudy E is "Bivalent BNT162b2 and BNT162b2 OMI."

Cohort 3 Design

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

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg

Participants 18 years of age and older who have received 3 prior 30-µg doses of BNT162b2, with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will receive a single 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) as a second booster dose (open-label). Approximately 400 participants will be enrolled into this cohort per Table 3.

Table 3. Cohort 3 Design

Cohort 3: BNT162b2 Bivalent (WT/OMI BA.4/BA.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization / Blind**
1	18-55 years	3	150-365 days	30 µg	200	Open-label
2	>55 years	3	150-365 days	30 µg	200	Open-label

Note: For certain safety and immunogenicity objectives, the 18- through 55-year age group and the >55-year age group will comprise participants from Cohorts 2 and 3 combined.

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Combining Cohort 2 and Cohort 3, there will be approximately 300 participants in each age group who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg. To evaluate the primary immunogenicity hypothesis for the >55-year age group of Cohort 2 and Cohort 3 combined, the participants >55 years of age from the C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group (approximately 300 participants [Expanded Enrollment – Group 1]).

Cohort 4: Participants 18 through 55 years of age who have received 3 or 4 prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being a bivalent vaccine at least 150 days prior to Visit 1 (Day 1), will be enrolled. The Cohort 4 bivalent vaccines target the SARS-CoV-2 Original strain and the Omicron variant (BA.4/BA.5 sublineage). The Cohort 4 monovalent vaccine targets the Omicron variant (BA.4/BA.5 sublineage). Participants will be randomized at a ratio of 1:1:1:1:1 to receive a single 30-µg dose of either BNT162b2 Bivalent, BNT162b5 Bivalent, BNT162b6 Bivalent, BNT162b7 Bivalent, or BNT162b7 Monovalent (observer-blind). Participants will be stratified by the number of prior doses (3 or 4 prior doses) of a US-authorized mRNA COVID-19 vaccine received prior to randomization.

Table 4. Cohort 4 Design

Cohort 4: BNT162b Omicron BA.4/BA.5 Vaccine Candidates All Participants 18 Through 55 Years of Age						
Group	**Study Intervention**	**Study Dose**	**Prior Doses of mRNA COVID-19 Vaccine**	**Time Since Last Dose**	**Number of Participants**	**Randomization / Blind**
1	BNT162b2 Bivalent (Original/OMI BA.4/BA.5)	30 µg	3 or 4	≥150 days	60	Randomized 1:1:1:1:1 Observer-blind
2	BNT162b5 Bivalent (Original/OMI BA.4/BA.5)	30 µg	3 or 4	≥150 days	60	
3	BNT162b6 Bivalent (Original/OMI BA.4/BA.5)	30 µg	3 or 4	≥150 days	60	
4	BNT162b7 Bivalent (Original/OMI BA.4/BA.5)	30 µg	3 or 4	≥150 days	60	
5	BNT162b7 Monovalent (OMI BA.4/BA.5)	30 µg	3 or 4	≥150 days	60	

4.2. Scientific Rationale for Study Design

The immune response following vaccination with BNT162b2 has been observed to wane with time, and a booster dose of BNT162b2 has demonstrated improvement in immune response, albeit to a lesser degree against some variants, particularly Omicron, of the original SARS-CoV-2 virus. The aim of the study is to improve the current protection elicited by BNT162b2.

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This is the first clinical study of BNT162b5 bivalent (Original/OMI BA.4/5), BNT162b6 bivalent (Original/OMI BA.4/5), and BNT162b7 monovalent and bivalent Omicron-modified vaccines. It was the first clinical study of BNT162b2 Bivalent (Original/OMI BA.4/BA.5) to evaluate the immune response to this new variant-targeted vaccine. Since the prevalence of Omicron sublineages remains high[13] following the EUA of BNT162b2 Bivalent (Original/OMI BA.4/BA.5), this study will now evaluate additional new bivalent vaccines targeting the ancestral strain and Omicron BA.4/BA.5 (BNT162b5 Bivalent, BNT162b6 Bivalent, and BNT162b7 Bivalent) and a new monovalent vaccine targeting Omicron BA.4/BA.5 alone (BNT162b7 Monovalent). The study design takes into account the similarity between the vaccines used in this study and the bivalent and monovalent vaccines currently being studied in C4591031 Substudy E (BNT162b2 Bivalent [WT/OMI BA.1] and BNT162b2 [OMI BA.1]) and that there have been no safety concerns to date with those vaccines. Likewise, the postauthorization use of BNT162b2 Bivalent (Original/OMI BA.4/BA.5) has not revealed any safety concerns to date. Prospective capture of confirmed COVID-19 cases with active COVID-19 surveillance and convalescent visits has been included.

4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants who align with the US population distribution (Census-based), in the age group of the study, to ensure that the study population is representative of patient populations that will benefit from a COVID-19 vaccine in clinical practice.

Given the relatively small size of the study, there may be less representation with respect to race, ethnicity, and geographic location.

4.2.2. Choice of Contraception/Barrier Requirements

BNT162b2 is approved for use without any contraceptive precautions. All investigational vaccines included in this study are RNA-LNP vaccines utilizing modRNA. While there is no suspicion of human teratogenicity based on the intended pharmacology, some of the variant vaccine components under evaluation have not been administered to humans before and, therefore, contraception requirements have been included in this protocol. See Appendix 4 for contraception requirements.

4.3. Justification for Dose

Based on data from the Phase 1 component of clinical trial C4591001 and available nonclinical data, the modRNA BNT162b2 vaccine candidate was selected at a dose of 30 µg for Phase 2/3 evaluation of safety, immunogenicity, and efficacy after 2 doses administered 3 weeks apart and is the authorized dose level for the third dose administered at least 5 months following the second dose. The 30-µg dose level of BNT162b2 was shown to be effective and has been approved in multiple countries worldwide for the primary 2-dose series as well as for third and fourth doses. BNT162b2 Bivalent (Original/OMI BA.4/BA.5)

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was granted EUA as a booster in the US at a 30-µg dose since 31 August 2022[7] and to be used for all doses, since 18 April 2023.[8]

Cohort 2 will also investigate a higher dose (60 µg) of BNT162b2 (WT/OMI BA.4/BA.5) in participants ≥18 years of age. Clinical trial C4591031 Substudy E is an ongoing study including participants 18 years of age and older who have previously received 3 doses of BNT162b2 (30-µg dose). A subset of participants in this substudy received BNT162b2 Bivalent (WT/OMI BA.1) at a total dose level of either 30 µg or 60 µg as a second booster dose. From the available safety data from the study, the reactogenicity profile of the variant vaccines was overall similar to the prototype BNT162b2 vaccine. In participants >55 years of age, who received monovalent and bivalent Omicron-modified vaccines at the 60-µg dose level, mild to moderate injection site pain, fatigue, and muscle pain were more common compared to the 30-µg dose level.[39] A subset of participants from C4591031 Substudy E (≥18 years of age) who received BNT162b2 (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be randomly selected to achieve the primary immunogenicity objective of Cohort 2.

4.4. End of Study Definition

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Ages for each cohort as follows:

   Cohort 1: Participants 18 through 55 years of age at randomization.

   Cohort 2: Participants ≥12 years of age at Visit 1.

   Cohort 3: Participants ≥18 years of age at Visit 1.

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Cohort 4: Participants 18 through 55 years of age at Visit 1.

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

Participant and Disease Characteristics:

2. Participants and participants' parent(s)/legal guardian(s), as appropriate, willing and able to comply with all scheduled visits/contacts, investigational plan, laboratory tests, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if indicated), 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.

Informed Consent:

4. Capable of giving signed informed consent/assent as described in Appendix 1, Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

   The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant's legal guardian (as defined in Appendix 1, Section 10.1.3) and the participant's assent, when applicable, before any study-specific activity is performed. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

Other Inclusion Criteria:

5. Cohort 1: Participants who have received 1 booster dose of a US-authorized COVID-19 vaccine, with the last prior dose being 90 or more days before Visit 1 (Day 1).

   Note: Documented confirmation of prior COVID-19 vaccines received must be obtained prior to randomization. All prior COVID-19 vaccines must be authorized for use in the US.

   Cohort 2 and Cohort 3: Participants who have received 3 prior doses of 30 µg BNT162b2, with the last dose being 150 to 365 days before Visit 1 (Day 1).

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Note: Documented confirmation of prior doses of BNT162b2 received must be obtained prior to randomization.

Cohort 4: Participants who have received 3 or 4 prior doses of a US-authorized mRNA COVID-19 vaccine (and dose level), with the last dose being a US-authorized Omicron BA.4/BA.5–adapted bivalent vaccine and dose level at least 150 days before Visit 1 (Day 1).

Note: Documented confirmation of prior mRNA COVID-19 vaccines received must be obtained before randomization. Participants must have received mRNA COVID-19 vaccines only.

5.2. Exclusion Criteria

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

Medical Conditions:

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

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

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

4. Women who are pregnant or breastfeeding.

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

Prior/Concomitant Therapy:

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

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

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

Prior/Concurrent Clinical Study Experience:

8. Participation in other studies involving receipt of a study intervention within 28 days before randomization. Anticipated participation in other studies involving a study intervention from randomization through the end of this study.

Other Exclusion Criteria:

9. 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.

Other Medical Conditions: From protocol amendment 6 (Cohort 4) onwards:

10. History of myocarditis or pericarditis.

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 from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use acceptable effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant or participant's parent(s)/legal guardian 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.

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5.4. Screen Failures

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

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

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

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

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

2. Current febrile illness (body 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 8.10.7).

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

3. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

4. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

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.

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6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to investigational product.

6.1. Study Interventions Administered

Cohort 1

- BNT162b5 Bivalent (WT/OMI BA.2) =
  BNT162b5 Wild Type and BNT162b5 OMICRON (B.1.1.529) sublineage BA.2
  (BNT162b5 RNA-LNP vaccine utilizing modRNA and encoding the P6' S)

- BNT162b2 Bivalent (WT/OMI BA.1) =
  BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.1
  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 1		
Intervention Name	BNT162b5 Bivalent (WT/OMI BA.2) (BNT162b5 Wild Type[a] and BNT162b5 OMICRON [B.1.1.529 sublineage BA.2]) Preformulated as a single vial (no dilution required)	BNT162b2 Bivalent (WT/OMI BA.1) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.1]) Preformulated as a single vial (no dilution required)
Arm Name (group of participants receiving a specific study intervention or no study intervention)	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Type	Vaccine	Vaccine
Dose Formulation	Multidose vial[b]	Multidose vial[b]
Unit Dose Strength(s)	100 µg/mL	100 µg/mL
Dosage Level(s)	30 µg (15 µg BNT162b5 Wild Type[a] and 15 µg BNT162b5 OMICRON [B.1.1.529 sublineage BA.2])	30 µg (15 µg BNT162b2 Wild Type[a] and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.1])
Route of Administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental and active comparator
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by Pfizer	Provided centrally by Pfizer

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Study Interventions – Cohort 1		
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Vials will be labeled as required per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Vials will be labeled as required per country requirement.

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the Original or reference strain.
b. Study intervention will be administered as a single dose from multidose vials.

Study Arms – Cohort 1		
Arm Title	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Arm Type	Experimental	Experimental and active comparator
Arm Description	Participants will receive 30 µg of BNT162b5 Bivalent (WT/OMI BA.2) at Visit 1.	Participants will receive 30 µg of BNT162b2 Bivalent (WT/OMI BA.1) at Visit 1.
Associated Intervention Labels	BNT162b5 Bivalent (WT/OMI BA.2) (BNT162b5 Wild Type and BNT162b5 OMICRON [B.1.1.529 sublineage BA.2])	BNT162b2 Bivalent (WT/OMI BA.1) (BNT162b2 Wild Type and BNT162b2 OMICRON [B.1.1.529 sublineage BA.1])

Cohort 2

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) = BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5 (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 2	
Intervention Name	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated as a single vial (no dilution required)
Arm Name (group of participants receiving a specific study intervention or no study intervention)	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)
Type	Vaccine
Dose Formulation	Multidose vial[b]
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg or 60 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) (30 µg BNT162b2 Wild Type and 30 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])
Route of Administration	Intramuscular injection

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Study Interventions – Cohort 2	
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Vials will be labeled as required per country requirement.

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the Original or reference strain.
b. Study intervention will be administered as a single dose from multidose vials.

Study Arms – Cohort 2					
Arm Title	Group 1: 12-17 years, 30 µg	Group 2: 18-55 years, 30 µg	Group 3: 18-55 years, 60 µg	Group 4: >55 years, 30 µg	Group 5: >55 years, 60 µg
Arm Type	Experimental	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg at Visit 1
Associated Intervention Label	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])				

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

Cohort 3

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) = BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5 (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 3	
Intervention Name	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated as a single vial (no dilution required)
Arm Name (group of participants receiving a specific study intervention or no study intervention)	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)
Type	Vaccine
Dose Formulation	Multidose vial[b]

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Study Interventions – Cohort 3	
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Vials will be labeled as required per country requirement.

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the Original or reference strain.
b. Study intervention will be administered as a single dose from multidose vials.

Study Arms – Cohort 3		
Arm Title	Group 1: 18-55 years of age, 30 µg	Group 2: >55 years of age, 30 µg
Arm Type	Experimental	Experimental
Arm Description	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1
Associated Intervention Label	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	

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

Cohort 4

The Cohort 4 bivalent vaccine names use “Original” instead of “Wild Type” (or “WT”). Both terms refer to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), which is also referred to in this protocol as the reference strain. Study intervention labeling may contain “Wild Type/WT” or “Original” interchangeably.

- BNT162b2 Bivalent (Original/OMI BA.4/BA.5) =
  BNT162b2 Original and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)
- BNT162b5 Bivalent (Original/OMI BA.4/BA.5) =
  BNT162b5 Original and BNT162b5 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b5 RNA-LNP vaccine utilizing modRNA and encoding the P6’ S)

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- BNT162b6 Bivalent (Original/OMI BA.4/BA.5) =
  BNT162b6 Original and BNT162b6 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b6 RNA-LNP vaccine utilizing modRNA for the P6 S)

- BNT162b7 Bivalent (Original/OMI BA.4/BA.5) =
  BNT162b7 Original and BNT162b7 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b7 RNA-LNP vaccine utilizing modRNA for the P6 S)

- BNT162b7 Monovalent (OMI BA.4/BA.5) =
  BNT162b7 OMICRON (B.1.1.529) sublineage BA.4/BA.5
  (BNT162b7 RNA-LNP vaccine utilizing modRNA for the P6 S)

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Study Interventions – Cohort 4					
Intervention Name	BNT162b2 Bivalent (Original/OMI BA.4/BA.5) (BNT162b2 Original[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated in a single vial (no dilution required)	BNT162b5 Bivalent (Original/OMI BA.4/BA.5) (BNT162b5 Original[a] and BNT162b5 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated in a single vial (no dilution required)	BNT162b6 Bivalent (Original/OMI BA.4/BA.5) (BNT162b6 Original[a] and BNT162b6 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated in a single vial (no dilution required)	BNT162b7 Bivalent (Original/OMI BA.4/BA.5) (BNT162b7 Original[a] and BNT162b7 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated in a single vial (no dilution required)	BNT162b7 Monovalent (OMI BA.4/BA.5) (BNT162b7 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated in a single vial (no dilution required)
Arm Name (group of participants receiving a specific study intervention or no study intervention)	BNT162b2 Bivalent (Original/ OMI BA.4/BA.5)	BNT162b5 Bivalent (Original/ OMI BA.4/BA.5)	BNT162b6 Bivalent (Original/OMI BA.4/BA.5)	BNT162b7 Bivalent (Original/ OMI BA.4/BA.5)	BNT162b7 Monovalent (OMI BA.4/BA.5)
Type	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine
Dose Formulation	modRNA	modRNA	modRNA	modRNA	modRNA
Unit Dose Strength(s)	100 µg/mL	100 µg/mL	100 µg/mL	100 µg/mL	100 µg/mL
Dosage Level(s)	30 µg (15 µg BNT162b2 Original and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	30 µg (15 µg BNT162b5 Original and 15 µg BNT162b5 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	30 µg (15 µg BNT162b6 Original and 15 µg BNT162b6 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	30 µg (15 µg BNT162b7 Original and 15 µg BNT162b7 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	30 µg (30 µg BNT162b7 OMICRON [B.1.1.529 sublineage BA.4/BA.5])
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Active comparator	Experimental	Experimental	Experimental	Experimental
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
Packaging and Labeling	Study intervention will be provided in multidose glass vials for single use as open-label supply. Vials will be labeled as required per country requirement.	Study intervention will be provided in multidose glass vials for single use as open-label supply. Vials will be labeled as required per country requirement.	Study intervention will be provided multidose glass vials for single use as open-label supply. Vials will be labeled as required per country requirement.	Study intervention will be provided in multidose glass vials for single use as open-label supply. Vials will be labeled as required per country requirement.	Study intervention will be provided in multidose glass vials for single use as open-label supply. Vials will be labeled as required per country requirement.

a. Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as Wild Type, WT, and the reference strain. Study intervention vial labels for the Cohort 4 bivalent vaccines may specify WT instead of Original.

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Study Arms – Cohort 4					
Arm Title	BNT162b2 Bivalent (Original/OMI BA.4/BA.5)	BNT162b5 Bivalent (Original/OMI BA.4/BA.5)	BNT162b6 Bivalent (Original/OMI BA.4/BA.5)	BNT162b7 Bivalent (Original/OMI BA.4/BA.5)	BNT162b7 Monovalent (OMI BA.4/BA.5)
Arm Type	Active comparator	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants will receive BNT162b2 Bivalent (Original/ OMI BA.4/BA.5) 30 µg at Visit 1.	Participants will receive BNT162b5 Bivalent (Original/ OMI BA.4/BA.5) 30 µg at Visit 1.	Participants will receive BNT162b6 Bivalent (Original/OMI BA.4/BA.5) 30 µg at Visit 1.	Participants will receive BNT162b7 Bivalent (Original/ OMI BA.4/BA.5) 30 µg at Visit 1.	Participants will receive BNT162b7 Monovalent (OMI BA.4/BA.5) 30 µg at Visit 1.
Associated Intervention Label	BNT162b2 Bivalent (Original[a]/OMI BA.4/BA.5) (BNT162b2 Original and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	BNT162b5 Bivalent (Original[a]/OMI BA.4/BA.5) (BNT162b5 Original and BNT162b5 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	BNT162b6 Bivalent (Original[a]/OMI BA.4/BA.5) (BNT162b6 Original and BNT162b6 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	BNT162b7 Bivalent (Original[a]/OMI BA.4/BA.5) (BNT162b7 Original and BNT162b7 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	BNT162b7 Monovalent (OMI BA.4/BA.5) (BNT162b7 OMICRON [B.1.1.529 sublineage BA.4/BA.5])

a. Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as Wild Type, WT, and the reference strain. Study intervention vial labels for the Cohort 4 bivalent vaccines may specify WT instead of Original.

6.1.1. Administration

Participants will receive 1 dose of study intervention as allocated by the IRT at Visit 1 in accordance with the study's SoA (Section 1.3).

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm. The volume to be administered may vary by dose level; full details are described in the IPM.

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 should be available in accordance with local guidelines for standard immunization practices.

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

Study intervention administration details will be recorded on the CRF.

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.

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

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

Study intervention will be prepared by qualified unblinded site personnel according to the IPM. The study intervention will be administered by unblinded study staff to all participants.

Study intervention will be provided in multidose vials; however, they are intended for single use, as outlined in the IPM.

6.3. Assignment to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system, including Group 1 of Cohort 2 (12 through 17 years of age) and the Cohort 3 groups, all receiving 30 µg of BNT162b2 Bivalent (WT/OMI BA.4/BA.5). Participants in Cohort 1 will be randomized 1:1 to receive either BNT162b5 Bivalent (WT/OMI BA.2) 30 µg or BNT162b2 Bivalent (WT/OMI BA.1) 30 µg. Participants 18 through 55 and >55 years of age in Cohort 2 will be randomized 1:1 within each age group to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either 30 µg or 60 µg. Participants in Cohort 4 will be randomized 1:1:1:1:1 (see Table 4). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the

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user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned vaccine group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Participants will be stratified in Cohort 1 by the number of months since the last dose of the COVID-19 vaccine received prior to entering the study (3 to 6 months [90 to 180 days] or >6 months [>180 days]). Participants will be stratified in Cohort 4 by the number of prior doses of a COVID-19 mRNA vaccine received (3 or 4 prior doses) prior to randomization.

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

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

6.4. Blinding

Cohort 1: This cohort will be observer-blind at the site level with respect to study intervention allocation and open-label to most Pfizer staff. Refer to Section 6.4.3.

Cohort 2: Participants 18 through 55 and >55 years of age receiving the second booster: These participant groups will be observer-blind at the site level with respect to study intervention allocation (dose of BNT162b2 [WT/OMI BA.4/BA.5]) and open-label to most Pfizer staff.

Participants 12 through 17 years of age receiving the second booster: This participant group is open-label. Refer to Table 1.

Cohort 3: Both participant groups (18 through 55 years of age and >55 years of age) receiving the second booster are open-label. Refer to Table 3.

Cohort 4: This cohort will be observer-blind at the site level with respect to study intervention allocation and open-label to most Pfizer staff.

6.4.1. Blinding of Participants

Cohort 1: Participants will be blinded to their assigned study intervention.

Cohort 2: Participants 12 through 17 years of age receiving the second booster will not be blinded to study intervention. Participants 18 through 55 and >55 years of age receiving the second booster will be blinded to the dose of BNT162b2 (WT/OMI BA.4/BA.5).

Cohort 3: All participants receiving the second booster will not be blinded to study intervention.

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Cohort 4: Participants will be blinded to their assigned study intervention.

Where applicable, participants will be unblinded at a time decided by Pfizer.

6.4.2. Blinding of Site Personnel

Although Cohort 2 has an open-label group (12 through 17 years of age receiving their second booster) and both Cohort 3 groups are open-label, the following instructions for site personnel applies to all participants in order to maintain the blinding for the other cohorts/groups:

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

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

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

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

6.4.3. Blinding of the Sponsor

Cohort 1, Cohort 2, and Cohort 4: To facilitate rapid review of data in real time, the majority of Pfizer/BioNTech staff will be unblinded to study intervention allocation.

Cohort 3: Given the single study intervention arm, both groups are unblinded to the majority of Pfizer staff involved in the conduct of the study.

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

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

6.4.4. Breaking the Blind

Emergency blind-break: 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 vaccine 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 vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, Pfizer 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.

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

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the unblinded 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 ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

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

6.6. Dose Modification

Not applicable to this study.

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.

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6.8. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose. In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs as medically appropriate and 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

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

- Prohibited medications listed in Section 6.9.1 will be recorded in the concomitant medication CRF, with the exception of prophylactic antipyretics and other pain medication to prevent symptoms.
- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit will be recorded in the nonstudy vaccination CRF.
- All prior COVID-19 vaccinations will be recorded in the prior COVID-19 vaccination CRF.
- Any prescribed medication to treat or intended to treat COVID-19/MIS-C illness, including receipt of antiplatelets (eg, aspirin, clopidogrel) or anticoagulants (eg, heparin, enoxaparin, warfarin), will be recorded in the concomitant medication CRF within the COVID-19 illness visit.

6.9.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward; however, it is anticipated that the participant would not be withdrawn from the study (unless documented as per Section 7.2). Medications should not be withheld if required for a participant's medical care.

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- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. With the exception of seasonal and pandemic influenza vaccine that can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

- 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: Chronic systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent.

- Receipt of systemic corticosteroids for <14 days is prohibited from 28 days prior to administration of study intervention and through 28 days after administration of study intervention.

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

- Receipt of any other (nonstudy) coronavirus vaccine at any time during study participation.

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

6.9.2. Permitted During the Study

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

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

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7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request or request of the participant's parent(s)/legal guardian. The participant will be permanently discontinued from the study at that time. Reasons for discontinuation from the study include the following:

- Lost to follow-up;
- Death;
- Study terminated by Pfizer;
- AEs;
- Participant/participant's parent(s)/legal guardian request;
- Investigator request;
- Select protocol deviations (Note: receipt of a COVID-19 vaccine outside of the study will result in study withdrawal).

If a participant withdraws from the study, they or the participant's parent(s)/legal guardian 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 Pfizer 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. Pfizer may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue active study participation (eg, biological sample collection or surveillance for disease endpoints) will remain in the study and must continue to be followed for protocol-specified safety follow-up procedures. The only exception to this is when a participant or participant's parent(s)/legal guardian specifically withdraws consent/assent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants or participants' parent(s)/legal guardian 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

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the medical records by the investigator, as to whether the withdrawal is only from specified study procedures and/or postvaccination safety 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 or participant's parent(s)/legal guardian and reschedule the missed visit as soon as possible. Counsel the participant or participant's parent(s)/legal guardian 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 or participant's parent(s)/legal guardian (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 or participant's parent(s)/legal guardian continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

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

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

A participant number will be assigned.

A randomization number and study intervention allocation will be obtained from the IRT system.

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

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

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

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

Safety and laboratory results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

The total blood sampling volume for individual participants at scheduled visits in this study is approximately 160 mL for participants ≥18 years of age and 50 mL for participants 12 through 17 years of age. Those participants ≥18 years of age in Cohort 2 who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of up to approximately 815 mL. Additionally, 20 mL of blood for participants ≥18 years of age and 10 mL for participants 12 through 17 years of age will be taken at an unplanned in-person potential COVID-19 illness visit and at an unplanned COVID-19 convalescent visit, conducted 28 to 35 days following the illness visit, with the illness visit completed at any time a participant develops symptoms indicating potential COVID-19. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days for participants 18 years of age and older.

8.1.1. Baseline Procedures

The baseline procedures (not detailed in subsequent sections) are listed below. They are performed at Visit 1 (Day 1):

- Record demography data (including date of birth, sex, race, and ethnicity).

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- Record any medical history of clinical significance, including confirmed COVID-19 diagnosis or asymptomatic positive SARS-CoV-2 test result (NAAT or antigen test).

- Measure and record height and weight.

8.2. Efficacy and/or Immunogenicity Assessments

8.2.1. Surveillance for COVID-19

Surveillance for potential cases of COVID-19 and MIS-C will occur throughout a participant's involvement in the study to describe both COVID-19 (all participants) and MIS-C (participants <21 years of age). If, at any time, a participant develops acute respiratory illness (see Section 8.10.7), for the purposes of the study he or she will be considered to potentially have COVID-19. In this circumstance, the participant or participant's parent(s)/legal guardian should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.10.8) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2

- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)

- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered as follows (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

    - Fever;

    - New or increased cough;

    - New or increased shortness of breath;

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- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

- The CDC list of COVID-19 symptoms can be found at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.[42] The additional symptoms listed by the CDC (ie, those not listed in the above protocol-defined list) should not trigger a potential COVID-19 illness visit unless, in the opinion of the PI, it is deemed necessary.

- Confirmed severe COVID-19 (FDA definition[43]): confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction;
  - Admission to an ICU;
  - Death.

- Confirmed severe COVID-19 (CDC definition[44]): confirmed COVID-19 and presence of at least 1 of the following:
  - Hospitalization;
  - Admission to the ICU;
  - Intubation or mechanical ventilation;
  - Death.

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The DMC may recommend modification of the definition of severe disease according to emerging information.

Confirmed MIS-C definition, as per the CDC MIS-C case definition[45]:

- An individual <21 years of age presenting with fever (≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours); AND
- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: Elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; AND
- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement:
    - Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia);
    - Renal (eg, AKI);
    - Respiratory (eg, pneumonia, ARDS, pulmonary embolism);
    - Hematologic (eg, elevated D-dimers, thrombophilia, or thrombocytopenia);
    - GI/hepatic (eg, elevated bilirubin, elevated liver enzymes, or diarrhea);
    - Dermatologic (eg, rash, mucocutaneous lesions);
    - Neurological (eg, CVA, aseptic meningitis, encephalopathy); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR
- COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

8.2.2. Vaccine-Induced Immunogenicity

Blood samples will be obtained at each visit for immunogenicity testing at the central laboratory. The following assays will be performed on serum samples at each visit:

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

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- SARS-CoV-2 neutralization assays (Omicron BA.1, Omicron BA.2, Omicron BA.4, Omicron BA.5; other variants), including other Omicron sublineages, may also be evaluated)

- At designated sites, optional whole blood samples of ~130 mL will be obtained from up to approximately 30 participants per group (≥18 years of age only) within Cohort 2 for evaluation of boostability and protection against Omicron and the reference strain for isolation of PBMCs. These samples will be used to describe B-cell and T-cell responses to Omicron and the reference strain. A blood sample of ~5 mL for HLA typing will also be obtained.

8.2.3. 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. These data will be used for study analyses.

8.2.4. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory analyst testing the samples will not know the participant's identity, study visit, or study cohort associated with the sample. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccines 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, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

The participant or participant's parent(s)/legal guardian 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, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

8.3. Safety Assessments

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

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8.3.1. Physical Examinations

Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed.

A complete physical examination will include evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

8.3.2. Vital Signs

The participant's body temperature will be measured at Visit 1, prior to study vaccination.

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

8.3.3. Clinical Safety Laboratory Assessments

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

8.3.4. Electronic Diary

Potential COVID-19 illness e-diary: This e-diary is used as a tool for participants to alert study sites of a COVID-19 diagnosis or symptoms that could represent a potential COVID-19 illness; it is not reported data. Participants will receive reminders to complete the COVID-19 illness e-diary on a weekly basis throughout the study and whenever they receive a diagnosis of COVID-19 or experience symptoms of COVID-19. Please refer to Section 8.2.1.

Reactogenicity e-diary: Participants or participants' parent(s)/legal guardian will be required to complete a reactogenicity e-diary through an application installed on a provisioned device or on the personal device of the participant or participant's parent(s)/legal guardian. All participants or participants' parent(s)/legal guardian will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days from the day of administration of the study intervention. Participants will receive reminders to complete the

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vaccination e-diary on a daily basis, starting on the day of vaccination (Day 1) through Day 7. 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. Generally, these data do not need to be reported by the investigator in the CRF as AEs. However, if a participant or participant's parent(s)/legal guardian withdraws because of events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant. If a participant missed reporting an event in the e-diary and reports it to the study site instead, the event should also be recorded on the AE page of the CRF.

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

The investigator or designee must obtain stop dates from the participant or participant's parent(s)/legal guardian 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.[46]

8.3.4.2. Local Reactions

During the reactogenicity e-diary reporting period, participants or participants' parent(s)/legal guardian will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant or participant's parent(s)/legal guardian will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at

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the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact 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 Pfizer. A Grade 4 reaction will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

Table 5. Local Reaction Grading Scale

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

a. Only an investigator or medically qualified person is able to classify a reaction as Grade 4; therefore, a confirmed Grade 4 reaction should be reported as an AE in the case report form.

8.3.4.3. Systemic Events

During the reactogenicity e-diary reporting period, participants or participants' parent(s)/legal guardian will be asked to assess vomiting, diarrhea, headache, fatigue/tiredness, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6.

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 Pfizer. A Grade 4 systemic event will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

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Table 6. 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

Abbreviation: IV = intravenous.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should be assessed by the investigator.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if the test result is positive, the symptoms should be recorded in the potential COVID-19 illness CRFs (with potential COVID-19 illness visit completed) rather than as systemic events in the reactogenicity e-diary (refer to Sections 8.10.7 and 8.10.8).

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8.3.4.4. Fever

In order to record information on fever, a thermometer will be given to participants or participants' parent(s)/legal guardian 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 of ≥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 7 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 Pfizer. Fevers >40.0°C (>104.0°F) will be collected as an AE on the CRF and assessed by the investigator using the AE intensity grading scale (Section 10.3.3).

Table 7. 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/Analgesic Medication

The use of antipyretic/analgesic 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. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at Visit 1, before the administration of the study intervention dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will not be administered the study intervention dose and will be withdrawn from the study.

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

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

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

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

During the active collection period as described in Section 8.4.1, each participant or participant's parent(s)/legal guardian 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 or participant's parent(s)/legal guardian 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 3 (approximately 1 month after the participant's study vaccination).

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

SAEs will be collected from the time the participant or participant's parent(s)/legal guardian provides informed consent through Visit 5 (approximately 6 months after the participant's study vaccination).

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

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

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

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If the participant or participant's parent(s)/legal guardian 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 the study because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported via PSSA or using the Vaccine SAE Report Form.

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period (through approximately 6 months after the participant's study vaccination) as described in Section 8.4.1 are reported to Pfizer Safety via PSSA or using the Vaccine SAE Report Form immediately upon awareness, and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant or participant's parent(s)/legal guardian.

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

8.4.2. Method of Detecting AEs and SAEs

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

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

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8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

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8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant within 28 days after receiving study intervention.
- A male participant inseminates a female partner within 28 days after receiving study intervention.
- 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 needlestick injury, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by needlestick injury, inhalation, or skin contact then exposes 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 or a participant's partner, the investigator must report this information to Pfizer Safety via PSSA or using the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the study intervention. Beyond 28 days after the study intervention, any pregnancy that occurs will not be considered EDP for this study.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety via PSSA or using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for

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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 within 28 days after receiving the 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 needlestick injury, inhalation, or skin contact.

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

A potential COVID-19/MIS-C illness visit, potential COVID-19 illnesses, and their sequelae should not be recorded as AEs, with the exception of those assessed by the investigator as related to the study intervention or those meeting the criteria for SAEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Through protocol amendment 2: Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

Note: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

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Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

From protocol amendment 4: All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety via PSSA or using the Vaccine SAE Report Form immediately upon awareness, and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. This includes potential COVID-19 illnesses and their sequelae that meet the definition of an SAE.

8.4.8. Adverse Events of Special Interest

Myocarditis and pericarditis, if reported, have additional procedures associated with their evaluation; they are, therefore, considered protocol-specified AESIs:

- Prior to Cohort 4: Confirmed diagnosis of myocarditis or pericarditis occurring within 4 weeks after vaccination. See Section 8.10.11.
- From Cohort 4 onwards: Confirmed diagnosis of myocarditis or pericarditis occurring within 6 weeks after vaccination. See Section 8.10.11.

Prior to Cohort 4: All AESIs must be reported as an AE or SAE following the procedures described in Section 8.4.1 through Section 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported via PSSA or using the Vaccine SAE Report Form.

From Cohort 4 onwards: Any diagnosis of myocarditis or pericarditis is considered an important medical event and must be reported as an SAE via PSSA or using the Vaccine SAE Report Form (refer to Section 8.4.1.1). Other diagnoses should be recorded as AEs or SAEs, as appropriate. Refer to Section 8.4.3 for information regarding follow-up of AEs and SAEs.

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.

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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

Not applicable.

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 via PSSA or on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the vaccination error	Only if associated with an SAE

Vaccination errors include:

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

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

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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 via PSSA or using a Vaccine SAE Report Form **only when associated with an SAE.**

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

Some of the blood samples collected for PBMC isolation and HLA typing may be used for DNA and/or RNA isolation. The DNA and/or RNA samples from the PBMC isolation may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. The DNA and/or RNA samples from the blood sample for HLA typing may be used to further characterize HLA type.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.2.

8.9. Health Economics

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

8.10. Study Procedures

8.10.1. Visit 1 – Study Intervention Administration – Day 1

- Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent and assent, if appropriate, will be obtained from the participant and/or participant's parent(s)/legal guardian. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant

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and/or participant's parent(s)/legal guardian. 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. Ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination and on the day of the vaccination.

- Assign a participant number using the IRT system. If the participant is from a prior Pfizer COVID-19 study, record the participant number of the prior study in the CRF. If the participant has participated in more than 1 prior Pfizer COVID-19 study, record the participant numbers of both the most recent prior study and the first study in the CRF.

- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

- Obtain medical history, including confirmed COVID-19 diagnosis or asymptomatic positive SARS-CoV-2 test result (NAAT or antigen test), and any other medical history of clinical significance.

- Review documentation of all prior COVID-19 vaccinations. All vaccines must be authorized for use in the US for participants enrolled in Cohort 1. All prior vaccines must be 30-µg doses of BNT162b2 for participants enrolled in Cohort 2 and Cohort 3. For Cohort 4, all prior vaccines must be mRNA vaccines (and dose levels) authorized for use in the US, with the last dose being a US-authorized Omicron BA.4/BA.5–adapted bivalent vaccine (and dose level).

- Perform a urine pregnancy test on WOCBP as described in Section 8.3.5.

- Discuss contraceptive use as described in Section 5.3.1.

- Measure the participant's height and weight.

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination (refer to Section 8.3.1), and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.

- Record nonstudy vaccinations as described in Section 6.9.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- On the day of and before vaccination, measure the participant's body temperature.

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- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- On the day of and before vaccination, obtain a nasal (midturbinate) swab (collected by site staff).
- On the day of and before vaccination, collect a blood sample (approximately 50 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age) for testing of immunogenicity and N-binding antibody.
- If the participant is part of the group for description of cell-mediated immune response (select sites only; Cohort 2 and ≥18 years of age only; additional consent required), collect a blood sample (approximately 130 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Site staff will obtain the participant's randomization number using the IRT system and will receive the randomization confirmation report.
- Site staff member(s) assigned to the "unblinded" role, per the delegation log, will obtain the vaccine vial allocation using the IRT. The vaccination visit confirmation report with the study intervention allocation will only be sent to site staff members in the "unblinded" role.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle, preferably of the nondominant arm. Please refer to the IPM for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Record AEs as described in Section 8.4.
- Explain the e-diary technologies available for this study (see Section 8.3.4) and assist the participant or participant's parent(s)/legal guardian in downloading the study application onto the participant's or participant's parent(s)/legal guardian's own device or issue a provisioned device if required.
- Provide instructions on e-diary completion and ask the participant or participant's parent(s)/legal guardian to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination (see Section 8.3.4.1 through Section 8.3.4.5).
- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

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- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Provide instructions on COVID-19 illness e-diary completion and ask the participant or participant's parent(s)/legal guardian to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.10.7 for further details. Provide instructions for use of the provided thermometer to monitor for fever (for COVID-19 surveillance).
- Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs or instruct the participant's parent(s)/legal guardian on the technique for collecting a nasal swab from their child at home.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.11).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or participant's parent(s)/legal guardian to bring the e-diary device to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

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- 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.

8.10.2. Visit 2 – 1-Week Follow-Up Visit (6 to 8 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.
- Record nonstudy vaccinations as described in Section 6.9.
- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.
- Record AEs as described in Section 8.4.
- Discuss contraceptive use as described in Section 5.3.1.
- Collect a blood sample (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only; Cohort 2 and ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day the reactogenicity e-diary was completed.
- If the 7-day reactogenicity period is ongoing: Remind the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.

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- Any severe systemic event.

- Remind the participant or participant's parent(s)/legal guardian 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 or participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any symptoms as detailed in Section 8.10.7.

- Ensure the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs or instruct the participant's parent(s)/legal guardian on the technique for collecting a nasal swab from their child at home.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.11).

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

- If the 7-day reactogenicity period is ongoing: Remind the participant or participant's parent(s)/legal guardian to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

- 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.

8.10.3. Visit 3 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.

- Record nonstudy vaccinations as described in Section 6.9.

- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.

- Record AEs as described in Section 8.4.

- Confirm contraceptive use as described in Section 5.3.1.

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- Collect a blood sample (approximately 50 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age) for immunogenicity testing.

- If the participant is part of the group for description of cell-mediated immune response (select sites only; Cohort 2 and ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.

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

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

- From Cohort 4 onwards: Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.11).

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any symptoms as detailed in Section 8.10.7.

- Ensure the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs or instruct the participant's parent(s)/legal guardian on the technique for collecting a nasal swab from their child at home.

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

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.10.4. Visit 4 – 3-Month Follow-Up Visit (84 to 98 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.

- Record nonstudy vaccinations as described in Section 6.9.

- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.

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- Record AEs as described in Section 8.4.
- Collect a blood sample (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age) for immunogenicity testing, unless advised otherwise by Pfizer.
- If the participant is part of the group for description of cell-mediated immune response (select sites only; Cohort 2 and ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.
- Remind the participant or participant's parent(s)/legal guardian 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 or participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any symptoms as detailed in Section 8.10.7.
- Ensure the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs or instruct the participant's parent(s)/legal guardian on the technique for collecting a nasal swab from their child at home.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.5. Visit 5 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.
- Record nonstudy vaccinations as described in Section 6.9.
- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.
- Record AEs as described in Section 8.4.
- Collect a blood sample (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age) for immunogenicity testing, unless advised otherwise by Pfizer.

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- If the participant is part of the group for description of cell-mediated immune response (select sites only; Cohort 2 and ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.

- Collect the participant's e-diary provisioned device or assist the participant or participant's parent(s)/legal guardian to remove the study application from his or her own personal device.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

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

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

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 or participant's parent(s)/legal guardian 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 that it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

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8.10.7. COVID-19 and MIS-C Surveillance

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution).

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

Note that:

- The CDC list of COVID-19 symptoms can be found at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.[42] The additional symptoms listed by the CDC (ie, those not listed in the above protocol-defined list) should not trigger a potential COVID-19 illness visit unless, in the opinion of the PI, it is deemed necessary.
- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required.
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to

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be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms that overlap with systemic reactogenicity events should be recorded in the reactogenicity e-diary or as AEs if not captured in the reactogenicity e-diary.

The participant or their parent(s)/legal guardian(s) are also instructed to contact the site immediately should the participant receive a positive SARS-CoV-2 test (NAAT or rapid antigen) result that is not accompanied by any symptoms. A potential COVID-19 visit is not required in this instance, but details of the positive test should be recorded in the designated CRF.

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.10.2) installed on a provisioned device or on the participant's or participant's parent(s)/legal guardian's own personal device to prompt him/her to report a diagnosis of COVID-19 or any symptoms of COVID-19. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

8.10.8. Potential COVID-19 Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant, the participant's parent(s)/legal guardian, and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.
- Record AEs as described in Section 8.4. Note: Potential COVID-19 illnesses should not be recorded as AEs, with the exception of those assessed by the investigator as related to study intervention or those meeting the criteria for SAEs.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab or instruct the participant's parent(s)/legal guardian to collect a nasal swab from their child at home and ship for assessment at the central laboratory.

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- If the visit is conducted in person, obtain a blood sample (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age), unless advised otherwise by Pfizer.

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:

  - Symptoms and signs, including

    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg).

    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg or requiring vasopressors).

    - Significant acute renal, hepatic, or neurologic dysfunction.

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO).

  - Clinical diagnosis.

  - Any prescribed medication to treat or intended to treat COVID-19/MIS-C illness. Refer to Section 6.9.

  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.

  - Full blood count.

  - Blood chemistry, specifically creatinine, urea, LFTs, and CRP.

  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction.

  - Number and type of any healthcare contact; duration of hospitalization and ICU stay.

  - Death.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

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8.10.9. Potential COVID-19 Convalescent Visit (28 to 35 Days After Potential COVID-19 Illness Visit)

This visit is to be completed 28 to 35 days after all potential COVID-19 illness visits. A separate blood sample is needed for this visit for testing purposes even if it coincides with another visit. No convalescent visits should be conducted after Visit 5 (6-month follow-up visit).

- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.10.8).
- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.
- Record AEs as described in Section 8.4. Note: Potential COVID-19 illnesses should not be recorded as AEs, with the exception of those assessed by the investigator as related to study intervention or those meeting the criteria for SAEs.
- Collect a blood sample (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age), unless advised otherwise by Pfizer.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.10. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visit 1: Contributes to the determination of a participant's baseline SARS-CoV-2 infection status.
- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Through protocol amendment 2: Research laboratory–generated results from the illness visit swabs will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Other research laboratory–generated results, including any positive vaccination visit swabs, will be provided to the site at the end of the study.

From protocol amendment 4: Research laboratory–generated results from the vaccination visit and illness visit swabs will be provided to the site at the end of the study only.

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Therefore, the participant or participant's parent(s)/legal guardian should be directed to seek additional testing through the participant's 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.

8.10.11. 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

- Prior to Cohort 4: within 4 weeks after the study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis.
- From Cohort 4 onwards: within 6 weeks after the study vaccination **must** be evaluated by a cardiologist 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:

- 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.

- Prior to Cohort 4: Any diagnosis made (eg, myocarditis, pericarditis, or other) should be recorded as an AE. Refer also to Section 8.4.8.
- From Cohort 4 onwards: Any diagnosis of myocarditis or pericarditis is considered an important medical event and must be reported as an SAE (refer to Section 8.4.1.1). Other diagnoses should be recorded as AEs or SAEs, as appropriate. Refer to Section 8.4.3 for information regarding follow-up of AEs and SAEs. Refer also to Section 8.4.8.

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8.10.12. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained, and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- A platform for recording local reactions and systemic events (reactogenicity e-diary); see Section 8.3.4.
- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).
- If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.
- Messages of thanks and encouragement from the study team.

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 Pfizer. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypothesis

Cohort 1, Cohort 2, and Cohort 4: For objectives evaluated separately within Cohort 1, Cohort 2, and Cohort 4, there is no formal hypothesis testing. All statistical analyses will be descriptive.

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Cohort 2 + Cohort 3 combined:

Superiority and Noninferiority of Anti-Omicron Immune Responses

For the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined):

The primary immunogenicity objective is to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group relative to the anti-Omicron immune response elicited by BNT162b2 30 µg in the >55-year age group from C4591031 Substudy E. The primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(1) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(1)$$

where ln(1) corresponds to a 1-fold margin for superiority and

  - $\text{Ln}(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2);

  - $\text{Ln}(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 in the >55-year age group from C4591031 Substudy E.

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.05 \text{ vs } H_1: p_1 - p_2 > -0.05$$

where -5% is the noninferiority margin for seroresponse and

  - p_1 Is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2);

  - p_2 Is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 in the >55-year age group from C4591031 Substudy E.

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

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Superiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 1; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

For the 18- through 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1 combined):

The primary immunogenicity objective is to assess the noninferiority with respect to level of neutralizing titer and seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18- through 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1) relative to the anti-Omicron immune response elicited by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2). The primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority and

  - $\text{Ln}(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18- through 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1);

  - $\text{Ln}(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2).

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.1 \text{ vs } H_1: p_1 - p_2 > -0.1$$

where -10% is the noninferiority margin for seroresponse and

  - p_1 Is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in 18- through 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1)

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- p_2 Is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 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.

Noninferiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

Noninferiority of Anti–Reference-Strain Immune Responses

The secondary immunogenicity objective is to assess the noninferiority of the anti–reference-strain immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group relative to the anti–reference-strain immune response elicited by BNT162b2 30 µg in the >55-year age groups. The noninferiority objective will be evaluated by the following hypothesis:

- The null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority and

- $\text{Ln}(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2);

- $\text{Ln}(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured at 1 month after BNT162b2 in the >55-year age group from C4591031 Substudy E.

Noninferiority based on the GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8.

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9.1.1. Estimands

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

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

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

9.1.2. Multiplicity Adjustment

Cohort 1, Cohort 2, and Cohort 4: No multiplicity adjustment is needed for objectives evaluated separately within Cohort 1, Cohort 2, and Cohort 4 as there are no statistical hypotheses.

Cohort 2 + Cohort 3 combined:

The primary and secondary objectives will be evaluated sequentially using a 1-sided alpha of 0.025. The primary objective for the >55-year age group will be evaluated first, followed by the secondary objective of the GMR for >55-year age group, and then the primary objective for the 18- through 55-year age group. The later objective will be evaluated only if the previous objective is met.

The primary objectives involve 2 hypotheses: GMR and seroresponse rate difference. Both hypotheses within the objective must be established before evaluating the next objective in the sequence. Therefore, the overall type I error is fully controlled.

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9.2. Analysis Sets

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

Population	Description
Screened	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized/assigned, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity (mITT)	All randomized/assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

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, secondary, and exploratory endpoints.

9.3.1. General Considerations

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

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

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

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9.3.1.1. Analyses for Binary Data

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

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

The primary approach to calculate the difference in seroresponse rate between 2 vaccine groups and the associated 95% CI will be based on the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median).

9.3.1.2. Analyses for Continuous Data

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

9.3.1.3. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t distribution, and then exponentiating the confidence limits.

Model-Based GMR:

As the primary approach, the GMR and associated 95% CI will be calculated by exponentiating the difference in LS means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model that includes terms for baseline neutralizing titer and comparison group.

Unadjusted GMR:

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

9.3.1.4. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points. GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated

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2-sided 95% CIs will be obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.5. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the left side of the step.

9.3.2. Primary Endpoints/Estimands Analysis

Endpoint	Statistical Analysis Methods
Safety	Cohort 1 and Cohort 4: • Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Local reactions and systemic events from Day 1 through Day 7 after the study vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after study vaccination will be provided for each vaccine group. Cohort 2 and Cohort 2 + Cohort 3 combined (30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age): • Reactogenicity, AEs, and SAEs will be summarized for each age group and vaccine dose-level group in the same way as described above for Cohort 1.
Immunogenicity	For each primary immunogenicity estimand described in Section 9.3.1, Cohort 1: At baseline and 1 month after the study vaccination: • GMTs and 2-sided 95% CIs will be provided for each vaccine group at each time point for SARS-CoV-2 Omicron (sublineages BA.1 and BA.2)–neutralizing and reference-strain–neutralizing titers. GMTs will be summarized in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.3.

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Endpoint	Statistical Analysis Methods
	• GMFRs of SARS-CoV-2 Omicron (sublineages BA.1 and BA.2)–neutralizing and reference-strain–neutralizing titers from baseline (before the study vaccination) to 1 month after the study vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group. GMFRs will be summarized in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.4. • The percentages of participants with seroresponse to Omicron (sublineages BA.1 and BA.2) and reference strain at 1 month after the study vaccination and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group. The percentages of participants with seroresponse will be summarized in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. • GMTs, GMFRs, and percentages of participants with seroresponse, along with the associated 95% CIs, will also be summarized by baseline SARS-CoV-2 infection status. Cohort 2: At baseline and 1 month after the study vaccination: • For each age group and vaccine dose-level group included in Cohort 2 and the selected subset of participants in the BNT162b2 (WT/OMI BA.1) 30-µg or 60-µg group from C4591031 Substudy E (≥18 years of age, see Section 4.1 for details), GMTs and GMFRs of SARS-CoV-2 Omicron (sublineages BA.1 and BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers, and percentages of participants with seroresponse to SARS-CoV-2 Omicron (sublineages BA.1 and BA.4/BA.5) and reference strain, along with the associated 95% CIs, will be summarized in the same way as described above for Cohort 1 and Cohort 4. Cohort 2 + Cohort 3 combined: For each primary immunogenicity objective described in Section 3 for Cohort 2 + Cohort 3 combined: • GMR of SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titer at 1 month after the study vaccination and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.3 in participants with and without evidence of SARS-CoV-2 infection. As the primary approach to calculate the GMR and CI for neutralizing titer, a linear regression model that includes terms for

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Endpoint	Statistical Analysis Methods
	baseline neutralizing titer and comparison group will be used to calculate the GMR and 95% CI, along with the model-based LS GMTs and associated 2-sided 95% CIs for each group. • The percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after the study vaccination will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method (see Section 9.3.1.1) in participants with and without evidence of SARS-CoV-2 infection. The primary approach to calculate the difference in seroresponse rate between 2 comparison groups and the associated 95% CI will be Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median). • For the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined), superiority based on GMR will be established if the model-based lower bound of the 2-sided 95% CI for GMR is greater than 1. Noninferiority based on seroresponse rate difference will be established if the lower bound of the 2-sided 95% CI for the difference in percentage is greater than -5%. • For the 18- through 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1 combined), noninferiority based on GMR will be established if the model-based lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. Noninferiority based on seroresponse rate difference will be established if the lower bound of the 2-sided 95% CI for the difference in percentage is greater than -10%. Cohort 4: At baseline and 1 month after the study vaccination: • GMTs and 2-sided 95% CIs of SARS-CoV-2 Omicron (sublineages BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers will be provided for each vaccine group at each time point, overall and by baseline SARS-CoV-2 infection status. Statistical methods are described in Section 9.3.1.3. • GMFRs of SARS-CoV-2 Omicron (sublineages BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers from baseline (before the study vaccination) to 1 month after the study vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group, overall and by baseline SARS-CoV-2 infection status. Statistical methods are described in Section 9.3.1.4.

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Endpoint	Statistical Analysis Methods
	• The percentages of participants with seroresponse to Omicron (sublineages BA.4/BA.5) and reference strain at 1 month after the study vaccination and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group, overall and by baseline SARS-CoV-2 infection status.

9.3.3. Secondary Endpoints

Endpoint	Statistical Analysis Methods
Immunogenicity	For the first secondary immunogenicity estimand described in Section 3 for Cohort 2 + Cohort 3 combined: • GMR of the SARS-CoV-2 reference-strain–neutralizing titer at 1 month after the study vaccination and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.3 in participants with and without evidence of SARS-CoV-2 infection. A linear regression model that includes terms for baseline neutralizing titer and comparison group will be used to calculate the GMR and 95% CI, along with the model-based LS GMTs and associated 2-sided 95% CIs for each comparison group. • Noninferiority will be established if the model-based lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: At baseline and 1 month after the study vaccination: • GMTs of SARS-CoV-2 Omicron (sublineages BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers and 2-sided 95% CIs will be provided for each age group at each time point. GMTs will be summarized in participants with and without evidence of SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.3. • GMFRs of SARS-CoV-2 Omicron (sublineages BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers from baseline (before the study vaccination) to 1 month after the study vaccination, along with the associated 2-sided 95% CIs, will be provided for each age group. GMFRs will be summarized in participants with and without evidence of SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.4.

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Endpoint	Statistical Analysis Methods
	• The percentages of participants with seroresponse to Omicron (sublineages BA.4/BA.5)– and reference-strain–neutralizing titers at 1 month after the study vaccination and the associated Clopper-Pearson 95% CIs will be provided for each age group. The percentages of participants with seroresponse will be summarized in participants with and without evidence of SARS-CoV-2 infection. • GMTs, GMFRs, and percentages of participants with seroresponse, along with the associated 95% CIs, will also be summarized by baseline SARS-CoV-2 infection status.

9.3.4. Exploratory Endpoints

Endpoint	Statistical Analysis Methods
Immunogenicity	Cohort 1: At baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination: • GMTs and GMFRs of SARS-CoV-2 Omicron (sublineages BA.1 and BA.2)–neutralizing and reference-strain–neutralizing titers, and percentages of participants with seroresponse to SARS-CoV-2 Omicron (sublineages BA.1 and BA.2) and reference strain, along with the associated 95% CIs, will be summarized in the same way as described above for the primary immunogenicity endpoints of Cohort 1. Cohort 2/Group 1, Cohort 2/Group 2 + Cohort 3/Group 1 combined, Cohort 2/Group 4 + Cohort 3/Group 2 combined, Cohort 2/Group 3, and Cohort 2/Group 5: At baseline and 1 month, 3 months, and 6 months after the study vaccination: • GMTs and GMFRs of SARS-CoV-2 Omicron (sublineages BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers, and percentages of participants with seroresponse to SARS-CoV-2 Omicron (sublineages BA.4/BA.5) and reference strain, along with the associated 95% CIs, will be summarized in the same way as described above for the primary immunogenicity endpoints of Cohort 1.

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Endpoint	Statistical Analysis Methods
	Cohort 4: At baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination: • GMTs and GMFRs of SARS-CoV-2 Omicron (sublineages BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers, and percentages of participants with seroresponse to SARS-CoV-2 Omicron (sublineages BA.4/BA.5) and reference strain, along with the associated 95% CIs, will be summarized in the same way as described above for the primary immunogenicity endpoints of Cohort 4.
COVID-19 cases	Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: • Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized for each vaccine and age group.
Immune response to SARS-CoV-2 infection	Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: • SARS-CoV-2–neutralizing titers at the time of a COVID-19 illness visit* and at the convalescent visit will be listed. (*Only for in-person COVID-19 visits.)
Immune response to other emerging variants (under monitoring, of interest, and/or of concern)	Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: • GMTs of SARS-CoV-2 variant–neutralizing titers for other variants (under monitoring, of interest, and/or of concern) not already specified, along with the associated 2-sided 95% CIs, will be provided at specific time points for each vaccine group. GMFRs from baseline (before the study vaccination) to each subsequent time point, and percentage of participants with seroresponse at each time point after vaccination, along with the associated 2-sided 95% CIs, may also be provided for each vaccine group.
Cell-mediated immune response	Cohort 2: • The cell-mediated immune response and additional humoral immune response parameters to the reference strain and Omicron variant will be summarized at each time point for the subset of participants with PBMC samples collected in each group.

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9.4. Interim Analyses

As C4591044 is a sponsor open-label, Phase 1/2/3 study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

No formal interim analysis will be conducted. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in Section 9.4.1.

9.4.1. Analysis Timing

Statistical analyses will be carried out when the following data are available for each of Cohort 1, Cohort 2, Cohort 2 + Cohort 3 combined, and Cohort 4:

- Safety and immunogenicity data through Visit 3 (1 month after study vaccination).
- Safety and immunogenicity data through Visit 5 (6 months after study vaccination).

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

9.5. Sample Size Determination

Cohort 1, Cohort 2, and Cohort 4: For the immunogenicity analyses conducted separately for Cohorts 1, 2, and 4, the sample size is not based on any formal hypothesis test. All statistical analyses will be descriptive.

For safety outcomes, Table 8 shows the probability of observing at least 1 AE for a given true event rate of a particular AE. For example, if the true AE rate is 2%, with 60, 100, 200, or 300 participants in a group, there is 70%, 87%, 98%, and >99% probability of observing at least 1 AE, respectively.

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

Assumed True Event Rate of an AE	N=60	N=100	N=200	N=300
0.1%	0.06	0.10	0.18	0.26
0.3%	0.16	0.26	0.45	0.59
0.5%	0.26	0.39	0.63	0.78
0.8%	0.38	0.55	0.80	0.91
1%	0.45	0.63	0.87	0.95
2%	0.70	0.87	0.98	>0.99
3%	0.84	0.95	>0.99	>0.99
4%	0.91	0.98	>0.99	>0.99
5%	0.95	0.99	>0.99	>0.99

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Cohort 2 + Cohort 3 combined: To provide sufficient power for the immunogenicity hypotheses for each of the age groups, the Cohort 2 18- through 55-year age and >55-year age groups receiving a 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) will be combined with the corresponding age and dose groups in Cohort 3.

Superiority and Noninferiority of Anti-Omicron Immunogenicity Objective

- For the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined vs BNT162b2 30-µg group from C4591031 Substudy E):

Assuming a 20% nonevaluable rate, with 300 participants >55 years of age receiving BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg (100 in Cohort 2/Group 2 and 200 in Cohort 3/Group 2) and 300 participants >55 years of age receiving BNT162b2 30 µg (from C4591031 Substudy E), approximately 480 evaluable participants (240 in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and 240 in the BNT162b2 30-µg group) will contribute to the immunogenicity evaluation. The superiority evaluation based on GMR and noninferiority evaluation based on seroresponse rate difference will each be performed at 1-sided alpha level of 0.025 as described in Section 9.1.2.

For comparisons based on GMR, common assay standard deviations at 1 month after the third or fourth dose in log scale is assumed to be 1.45 based on data observed in the C4591031 Substudy E. If the true GMR of Omicron–neutralizing titer in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group to the BNT162b2 30-µg group is 1.5, then 480 evaluable participants will provide 86.4% power to declare noninferiority.

For comparisons based on seroresponse rate difference, if the seroresponse rate is 65% in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and 52% in the BNT162b2 30-µg group, the study has 98.0% power to demonstrate noninferiority using a 5% margin.

- For the 18- through 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1 combined) vs >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined):

Assuming a 20% nonevaluable rate, with 300 participants receiving BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18- through 55-year age group (100 in Cohort 2/Group 2 and 200 in Cohort 3/Group 1) and 300 participants receiving BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group (100 in Cohort 2/Group 4 and 200 in Cohort 3/Group 2), approximately 240 evaluable participants in each age group (18- through 55-year age group and >55-year age group) will contribute to the immunogenicity evaluation. The noninferiority evaluation based on GMR and seroresponse rate difference will each be performed at 1-sided alpha level of 0.025 as described in Section 9.1.2.

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For comparisons based on GMR, common assay standard deviations at 1 month after the third or fourth dose in log scale is assumed to be 1.45 based on data observed in the C4591031 Substudy E. If the true GMR of Omicron–neutralizing titer after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18- through 55-year age group to the >55-year age group is 1, then 480 evaluable participants (240 in the 18- through 55-year age group and 240 in the >55-year age group) will provide 86.4% power to declare noninferiority.

For comparisons based on seroresponse rate difference, if the seroresponse rate after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg is 65% in the 18- through 55-year age group and 65% in the >55-year age group, the study has 63.4% power to demonstrate noninferiority using a 10% margin.

Noninferiority of Anti–Reference-Strain Immunogenicity Objective

For comparisons based on GMR, common assay standard deviations at 1 month after the third or fourth dose in log scale is assumed to be 1.05 based on data observed in the C4591031 Substudy E. If the true GMR of reference-strain–neutralizing titer after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg to after BNT162b2 30 µg in the >55-year age group is 1, then 480 evaluable participants (240 in the BNT162b2 Bivalent [WT/OMI BA.4/BA.5] 30-µg group and 240 in the BNT162b2 30-µg group) will provide 98.8% power to declare noninferiority using a 1.5-fold margin.

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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.

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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 Pfizer with sufficient, accurate financial information as requested to allow Pfizer 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/Assent Process

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

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited, they cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide their own assent, the source documents must record why the participant did not provide assent (for example, the child is not of assenting age per local regulations or policies), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority or if a child reaches the age of assent (per local IRB/EC requirements) during the study, as recognized under local law, the child or adolescent must then provide the appropriate assent or consent to document their willingness to continue in the study. For an adolescent who reaches the age of consent, parental consent would no longer be valid. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, the participant must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants must be informed that their participation is voluntary. Participants and/or the participant's parent(s)/legal guardian 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.

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The investigator must ensure that each participant and/or his/her parent(s)/legal guardian 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 and/or his/her parent(s)/legal guardian must be informed that the participant's 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 and/or his/her parent(s)/legal guardian.

The participant and/or his/her parent(s)/legal guardian must be informed that the participant's 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 and/or his/her parent(s)/legal guardian is fully informed about their right to access and correct the participant's personal data or their child's personal data and to withdraw consent for the processing of the participant's personal data or their child's personal data.

The source documentation must include a statement that written informed consent and as applicable, assent, was obtained before the participant was enrolled in the study and the date on which the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants and/or the participant's parent(s)/legal guardian must be reconsented to the most current version of the IRB/EC-approved ICD(s)/assent during their participation in the study as required per local regulations.

A copy of the ICD(s) and assent(s) must be provided to the participant and/or his/her parent(s)/legal guardian.

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.

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

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

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

10.1.6. Dissemination of Clinical Study Data

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

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

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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.

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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 form and are password protected to prevent access by unauthorized third parties.

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

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

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

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

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

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

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

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10.1.8. Source Documents

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

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

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

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

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

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

10.1.9. 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 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;

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- Discontinuation of further study intervention development.

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

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

10.1.10. Publication Policy

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

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

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

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have

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access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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

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

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

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

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

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

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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 1 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.

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

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- 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 PSSA/the Vaccine SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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.

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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 1 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 PSSA or the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

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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, PSSA or eSAE). • 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 offline 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 offline, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

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

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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.

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.

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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 1 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.

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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.

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Sexual Abstinence

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

Other Effective Methods

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

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

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

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis.

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

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

- The samples will be retained as indicated:

  - Samples for specified genetic analysis (see Section 8.6) will be stored for up to 15 years or other period as per local requirements.

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

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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 for all participants 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).

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- 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 Pfizer.

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.

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10.7. Appendix 7: Kidney Safety Monitoring Guidelines

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

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

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

10.7.2. Age-Specific Kidney Function Calculation Recommendations

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

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

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

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

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10.8. Appendix 8: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 1 (27 July 2022)

Overall Rationale for the Amendment:

Inclusion of a second cohort to describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg in individuals ≥12 years of age and at 60 µg in adults ≥18 years of age. Added corresponding objectives, estimands, and endpoints and details in the statistical methods sections. Study intervention details and background information supporting inclusion of this cohort were added.

Inclusion of prospective capture of confirmed COVID-19 cases for both Cohorts 1 and 2 with active COVID-19 surveillance and convalescent visits.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 Synopsis	Updated the text with respect to the addition of Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in participants 12 years of age and above and 60 µg in participants 18 years of age and above.	Substantial
Section 1.2 Schema	Added Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 1.3 Schedule of Activities	Added text to include PBMC and HLA sampling in Cohort 2. Added blood volume for participants 12 through 17 years of age. Added reminder to obtain assent for pediatric population.	To describe B-cell and T-cell responses to Omicron and the reference strain. To accommodate reduced blood draw volume for the younger age group. To reflect changed informed consent process for pediatric population of Cohort 2.	Substantial
Section 2 Introduction	Added text to provide background on the emergence of additional Omicron sublineages; added rationale for the addition of Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 3 Objectives, Endpoints, and Estimands	Updated the text with respect to the addition of Cohort 2.	To describe the analysis of data from Cohort 2.	Substantial
Section 4 Study Design	Updated the text with respect to the addition of Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 5.1 Inclusion Criteria	Updated inclusion criteria 1, 2, 4, and 5 with respect to the addition of Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 6 Study Intervention(s) and Concomitant Therapy	Updated the text with respect to the addition of Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 6.4 Blinding	Updated the text with respect to the addition of Cohort 2.	To describe the change in blinding for Cohort 2.	Substantial
Section 8 Study Procedures	Added text to include PBMC and HLA sampling in Cohort 2. Added text regarding the total blood sampling volume for participants providing these optional samples. Added text regarding the total blood sampling volume for participants 12 through 17 years of age.	To describe B-cell and T-cell responses to Omicron and the reference strain. To accommodate reduced blood draw volume for the younger age group.	Substantial
Section 9.3.4 Exploratory Objectives	Updated the text with respect to the addition of Cohort 2.	To describe the analysis of data from Cohort 2	Substantial
Section 10.5 Genetics	Added Section 10.5 because of the inclusion of PBMC sampling in Cohort 2.	To describe B-cell and T-cell responses to Omicron and the reference strain.	Substantial
Section 1.1 Synopsis	Updated the exploratory objectives and endpoints to include confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group, with respect to COVID-19 surveillance.	To describe the analysis of data from COVID-19 surveillance.	Substantial
Section 1.2 Schema	Added COVID-19 Surveillance.	To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.	Substantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.3 Schedule of Activities	Added text with respect to COVID-19 surveillance and activities related to potential COVID-19 illness visits and convalescent visits. This includes provision of nasal self-swab kits and instructions on self-collection of nasal swabs. Included statement that any AEs occurring within 48 hours of nasal swab collection should be reported. Because of inclusion of the illness e-diary, deletion of the e-diary application or collection of the provisioned device was moved from the 1-month follow-up visit to the 6-month follow-up visit.	To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.	Substantial
Section 3 Objectives, Endpoints, and Estimands	Updated the exploratory objectives and endpoints to include confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group, with respect to COVID-19 surveillance.	To describe the analysis of data from COVID-19 surveillance.	Substantial
Section 4.2 Scientific Rationale	Updated the text with respect to COVID-19 surveillance.	To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.	Substantial
Section 8 Study Procedures	Updated the text with respect to COVID-19 surveillance and procedures related to potential COVID-19 illness visits and convalescent visits. Because of inclusion of the illness e-diary, deletion of the e-diary application or collection of the provisioned device was removed from the 1-week and 1-month follow-up visits to the 6-month follow-up visit.	To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.	Substantial
Section 8.4.8 Adverse Events of Special Interest	Updated to remove confirmed COVID-19 diagnosis as an AESI.	To include COVID-19 illness visits. To capture COVID-19 within that data set and not to duplicate it as an AE.	Substantial
Section 9.3.4 Exploratory Endpoints	Updated with respect to exploratory objective and endpoints for COVID-19 surveillance.	To describe the analysis of data from COVID-19 surveillance.	Substantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.3 Schedule of Activities	Removed allowance for Visit 1 to be conducted over 2 consecutive days.	To align with recruitment expectations and visit scheduling.	Nonsubstantial
Section 4.2.2 Choice of Contraception/Barrier Requirements	Updated the text with respect to the addition of Cohort 2.	To clarify the requirement for contraception.	Nonsubstantial
Section 5.5 Temporary Delay Criteria	Replaced "oral temperature" with "body temperature." The temperature measurement route is per investigator discretion.	To align with Sections 1.3 (Schedule of Activities), 8.3.2 (Vital Signs), and 8.10.1 (Visit 1 study procedures).	Nonsubstantial
Section 6.3 Assignment to Study Intervention	Added day range to strata.	To clarify stratification.	Nonsubstantial
Section 8.10.1 Visit 1 – Study Intervention Administration – Day 1	Removed the allowance for Visit 1 to be conducted over 2 consecutive days.	To align with recruitment expectations and visit scheduling.	Nonsubstantial
All	Administrative corrections to formatting, typographical errors, and naming of "Pfizer," where necessary.	Administrative correction.	Nonsubstantial
Section 11 References	Updated with respect to text added per protocol amendment 1 changes.	To record additional references.	Nonsubstantial

Amendment 2 (24 August 2022)

Overall Rationale for the Amendment:

Inclusion of a third cohort to allow for a sufficiently powered evaluation of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster dose in BNT162b2-experienced participants ≥18 years of age. Added corresponding objectives, estimands, and endpoints and details in the statistical methods sections. Study intervention details and background information supporting inclusion of this cohort were added.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Cover page	Amended the title to remove blinding level and to change from Phase 2 to Phase 2/3. Corrected Study Intervention Name to reflect 'BNT162b'.	With addition of Cohort 3, the mix of blinding levels by cohort is detailed in Sections 4.1 and 6.4.	Substantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 4.2 Scientific Rationale for Study Design	Updated to include Phase 3 per title change.	Cohort 3 is considered a Phase 3 study, consistent with how we have described prior variant vaccine evaluations in 300 participants per group.	
Section 1.1 Synopsis	Updated rationale on prevalence of Omicron BA.4 and BA.5 sublineages.	To reflect the evolving pandemic and medical need for prevention of Omicron BA.4 and BA.5 sublineages.	Substantial
Section 1.1 Synopsis	Updated text with respect to the addition of Cohort 3, including the protocol title.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 1.2 Schema	Added Cohort 3.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 1.3 Schedule of Activities	Noted that PBMC sampling and HLA typing are not applicable for Cohort 3.	Cohort 3 is not part of the PBMC subset.	Substantial
	Added blood sample collection in the potential COVID-19 illness visit for participants who have this visit in person.	To comply with regulatory agency requests.	
Section 2 Introduction	Updated text on the prevalence of Omicron BA.4 and BA.5 sublineages.	To reflect the evolving pandemic and medical need for prevention of Omicron BA.4 and BA.5 sublineages.	Substantial
Section 3 Objectives, Endpoints, and Estimands	Updated to reflect the addition of Cohort 3.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
	For the Cohort 2 primary immunogenicity objective, added clarification to the selection of comparator participants from C4591031 Substudy E.	To comply with regulatory agency requests.	

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 4.1 Overall Design	Updated to reflect the addition of Cohort 3.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
	For the Cohort 2 primary immunogenicity objective, added clarification to the selection of comparator participants from C4591031 Substudy E.	To comply with regulatory agency requests.	
Section 5.1 Inclusion Criteria	Updated to reflect the addition of Cohort 3.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 6 Study Interventions	Updated to reflect the addition of Cohort 3.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 8.1 Administrative and Baseline Procedures	Clarifications made to blood volumes and added blood sample for in-person potential COVID-19 illness visits.	To comply with regulatory agency requests and clarify volume calculations.	Substantial
Section 8.10.8 Potential COVID-19 Illness Visit	Added blood sample collection in the potential COVID-19 illness visit for participants who have this visit in person.	To comply with regulatory agency requests.	Substantial
Section 9 Statistical Considerations	Updated to reflect the addition of Cohort 3 and its associated analyses.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 5.2 Exclusion Criteria	Clarifications.	In response to site inquiries and for alignment with other C459 studies.	Nonsubstantial
Section 6 Study Interventions and Concomitant Therapy	Added: “For the purposes of this protocol, study intervention refers to investigational product”	Content was added to match current protocol template.	Nonsubstantial
Section 6.9.1 Prohibited During the Study	Clarifications.	In response to site inquiries and for alignment with other C459 studies.	Nonsubstantial
Section 8.2.1 Surveillance for COVID-19	Title of section updated.	Title updated to better reflect objective.	Nonsubstantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 8.3.4.3 Systemic Events	Corrected instructions explaining what should occur in the event of a local positive SARS-CoV-2 test in a symptomatic participant.	To align with sections 8.4.8, 8.10.7 and 8.10.8.	Nonsubstantial
Section 8.3.4.4 Fever	Edits made to Table 7: Scale for Fever.	To align how Celsius temperature ranges were presented with FDA reference and content within section.	Nonsubstantial
Section 8.4.5.1 Exposure During Pregnancy	Updated to reflect study definition of Exposure During Pregnancy as per other content within section.	Updated to maintain consistency within section.	Nonsubstantial
All	Minor editorial changes.	Corrections or minor edits in line with amendment updates.	Nonsubstantial

Amendment 3 (14 April 2023)

Protocol amendment 3 was created but not implemented. The next amendment (protocol amendment 4) was developed from protocol amendment 2.

Amendment 4 (26 May 2023)

Overall Rationale for the Amendment:

Inclusion of a fourth cohort to describe the immune response to authorized and new 30-µg bivalent and monovalent Omicron BA.4/BA.5–modified BNT162b vaccines:

- BNT162b2 Bivalent (Original/OMI BA.4/BA.5)
- BNT162b5 Bivalent (Original/OMI BA.4/BA.5)
- BNT162b7 Bivalent (Original/OMI BA.4/BA.5)
- BNT162b7 Monovalent (OMI BA.4/BA.5)

given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age. Added corresponding objectives, estimands, and endpoints and details in the statistical methods sections. Study intervention details and background information supporting the inclusion of this cohort were also added.

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Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Cover page, synopsis, and sections referring to phase of study	Added "Phase 1."	This study is considered Phase 1/2 for the cohorts evaluating BNT162b5 bivalent and BNT162b7 bivalent and monovalent.	Substantial
Cover page	Added IND number 29525.	Per feedback from FDA/CBER, BNT162b7 is considered a new vaccine and, as such, clinical studies should be conducted under a new IND.	Substantial
Protocol Summary: Section 1.1, Section 1.2 and Section 1.3	Updated text, tables, and schema with respect to the addition of Cohort 4.	To obtain data on the authorized and new 30-µg bivalent and monovalent Omicron BA.4/BA.5–modified BNT162b vaccines in participants 18 through 55 years of age.	Substantial
Section 2 Introduction	Added text to provide background and rationale for the addition of Cohort 4.	To obtain data on the new 30-µg bivalent and monovalent BNT162b vaccines.	Substantial
Section 1.1 and Section 3 Objectives, Endpoints, and Estimands	Updated the text with respect to the addition of Cohort 4.	To describe the analysis of data from Cohort 4.	Substantial
Section 3 Objectives, Endpoints, and Estimands	Updated the primary immunogenicity estimands for Cohort 1.	To specify the analysis time points for the primary immunogenicity analysis and to move the Day 7 time point to exploratory objectives to reflect the final analysis.	Substantial
Section 3 Objectives, Endpoints, and Estimands	Updated the primary immunogenicity estimands for Cohort 2.	To retain the primary endpoint time point in primary objective (1-month time point) and to move the analysis at the rest of the time points to exploratory objectives to reflect the final analysis.	Substantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 3 Objectives, Endpoints, and Estimands	Merged the immunogenicity objectives of Cohort 2 and Cohort 3 and select subsets of 100 participants each from Cohort 2/Group 2 + Cohort 3/Group 1 combined, Cohort 2/Group 4 + Cohort 3/Group 2 combined, and the C4591031 Substudy E expanded-cohort BNT162b2 30-µg group for the final analysis.	To combine Cohort 2 and Cohort 3 immunogenicity data to reflect the final analysis.	Substantial
Section 3 Objectives, Endpoints, and Estimands	Updated the immunogenicity estimands for the Cohort 2 + Cohort 3 combined analysis.	To split out the 1-month analysis to reflect the analysis performed for the interim CSR.	Substantial
Section 4 Study Design	Added Cohort 4–specific information to Sections 4.1, 4.2, and 4.3.	Updated for the addition of Cohort 4.	Substantial
Section 5.1 Inclusion Criteria	Added Cohort 4–specific inclusion criteria.	Updated for the addition of Cohort 4.	Substantial
Section 6.1 Study Interventions Administered	Added the Cohort 4 vaccines and study intervention details.	Updated for the addition of Cohort 4.	Substantial
Section 6.3 Assignment to Study Intervention	Added the Cohort 4 randomization scheme.	Updated for the addition of Cohort 4.	Substantial
Section 6.4.1 Blinding of Participants	Added text to specify the unblinding time point.	The unblinding time point was established for Cohorts 1 and 2 and anticipated for Cohort 4.	Substantial
Section 6.4.4 Breaking the Blind	Added text to distinguish emergency unblinding procedures and nonemergency unblinding procedures (Pfizer unblinding time point).	The unblinding time point was established for Cohorts 1 and 2 and anticipated for Cohort 4.	Substantial
Section 8.4.7 Disease-Related Events and/or Disease Related Outcomes Not	Revised text to indicate that study swab results will now be released to investigators at the end of the study only.	Change to information related to release of study swab results. Change to SAE reporting requirements for	Substantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Qualifying as AEs or SAEs Section 8.10.10 SARS-CoV-2 NAAT Results		potential COVID-19 illness cases in line with this change to the release of results.	
Section 8.10.1 Study procedures for Visit 1	Added prior COVID-19 vaccines documentation for Cohort 4.	To update for the addition of Cohort 4.	Substantial
Section 9.3.2 Primary Endpoints/Estimands Analysis	Updated Section 9.3.2 to align with the changes to the objectives. Added Cohort 4.	To update to reflect the final analysis. To describe the analysis of data from Cohort 4.	Substantial
Section 9.3.3 Secondary Endpoints	Updated Section 9.3.3 to align with the changes to the objectives.	To update to reflect the final analysis.	Substantial
Section 9.3.4 Exploratory Endpoints	Updated Section 9.3.4 to align with the changes to the objectives. Added Cohort 4.	To describe the analysis of data from Cohort 4.	Substantial
Section 9.5 Sample Size Determination	Added Cohort 4.	To obtain data on authorized and new 30-µg bivalent and monovalent Omicron BA.4/BA.5–modified BNT162b vaccines.	Substantial
Section 9.4 Interim Analysis	Updated to reflect that the study is Phase 2/3 and open-label to the sponsor.	To clarify and to support the change made to Section 9.4.1 per the PACL dated 15 Feb 2023.	Nonsubstantial
Section 9.4.1 Analysis Timing	Clarified that additional analyses may be conducted and analyses may be combined.	To permit analyses to inform product development and/or for program-level decisions per the PACL dated 15 Feb 2023.	Nonsubstantial
Section 10.8 Appendix 8: Protocol Amendment History	Added Amendment 2 summary of changes.	Protocol template requirement.	Nonsubstantial
Section 10.9 Appendix 9: Abbreviations	Updated with vaccines for Cohort 4.	Administrative updates for the Cohort 4 addition to the protocol.	Nonsubstantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 11 References	Updated with respect to text added per protocol amendment 4 changes.	To record additional references.	Nonsubstantial
Various sections	Made minor clarifications and editorial changes.	Edits to improve clarity and administrative corrections.	Nonsubstantial

Amendment 5 (23 June 2023)

Protocol amendment 5 was created but not implemented. The next amendment (protocol amendment 6) was developed from protocol amendment 4.

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10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BCR	B-cell receptor
β-hCG	β-human chorionic gonadotropin
BNP	brain natriuretic peptide
BNT162b2 Bivalent (WT/OMI BA.1)	BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529 sublineage BA.1)
BNT162b2 Bivalent (Original/OMI BA.4/BA.5)	BNT162b2 Original and BNT162b2 OMICRON (B.1.1.529 sublineage BA.4/BA.5)
BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529 sublineage BA.4/BA.5)
BNT162b5 Bivalent (Original/OMI BA.4/BA.5)	BNT162b5 Original and BNT162b5 OMICRON (B.1.1.529 sublineage BA.4/BA.5)
BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b5 Wild Type and BNT162b5 OMICRON (B.1.1.529 sublineage BA.2)
BNT162b6 Bivalent (Original/OMI BA.4/BA.5)	BNT162b6 Original and BNT162b6 OMICRON (B.1.1.529 sublineage BA.4/BA.5)
BNT162b7 Bivalent (Original/OMI BA.4/BA.5)	BNT162b7 Original and BNT162b7 OMICRON (B.1.1.529 sublineage BA.4/BA.5)
BNT162b7 Monovalent (OMI BA.4/BA.5)	BNT162b7 OMICRON (B.1.1.529 sublineage BA.4/BA.5)
CBER	Center for Biologics Evaluation and Research (United States)
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
ChAdOx1-S	ChAdOx1-S (recombinant) SARS-CoV-2 vaccine (AstraZeneca)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration

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Abbreviation	Term
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRE	disease-related event
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
ESR	erythrocyte sedimentation rate
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)
FIH	first-in-human
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GMFR	geometric mean fold rise

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Abbreviation	Term
GMR	geometric mean ratio
GMT	geometric mean titer
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ID	identification
IgG	immunoglobulin G
IL-6	interleukin 6
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	institutional review board
IRT	interactive response technology
KDIGO	Kidney Disease: Improving Global Outcomes
LDH	lactate dehydrogenase
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LS	least square
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
mRNA-1273	mRNA-1273 SARS-CoV-2 vaccine (Moderna)
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding

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Abbreviation	Term
NIMP	noninvestigational medicinal product
OMI	Omicron
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
P6 S	SARS-CoV-2 full-length, P6 mutant, prefusion spike glycoprotein
P6' S	SARS-CoV-2 full-length, P6 prime mutant, prefusion spike glycoprotein
PACL	protocol administrative change letter
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PI	principal investigator
PPE	personal protective equipment
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QTL	quality tolerance limit
RBD	receptor binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
Scr	serum creatinine
Scys	serum cystatin C
SI	study intervention
SmPC	summary of product characteristics
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
T bili	total bilirubin
TCR	T-cell receptor
Th1	T-helper type 1
UK	United Kingdom
ULN	upper limit of normal
US	United States

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Abbreviation	Term
USPI	US prescribing information
Vax	vaccination
VE	vaccine efficacy
WOCBP	woman/women of childbearing potential
WT	wild type

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