A PHASE 2/3 PROTOCOL TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF BNT162b2 RNA-BASED VACCINE CANDIDATES FOR SARS-CoV-2 NEW VARIANTS IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech SE
Study Conducted by:	Pfizer Inc.
Study Intervention Number:	PF-07302048
Study Intervention Name:	BNT162b2 RNA-Based COVID-19 Vaccine
US IND Number:	19736
EU CT Number:	Not applicable
ClinicalTrials.gov ID:	NCT05997290
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C4591054
Phase:	2/3
Sponsor's Agent's Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

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

Document History

Document	Version Date
Amendment 2	07 August 2024
Amendment 1	11 March 2024
Original protocol	18 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 change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 2 (07 August 2024)

Overall Rationale for the Amendment:

This amendment adds Cohort 3 to Substudy C for the evaluation of BNT162b2 (Omi KP.2) in response to the US FDA/CBER's recommendation on 13 June 2024 for updated COVID-19 vaccines to target the Omicron KP.2 strain, if feasible. Participants 18 years of age and older will be enrolled into Cohort 3 for the evaluation of the safety, tolerability, and immunogenicity of BNT162b2 (Omi KP.2). Cohorts 1 and 2, evaluating BNT162b2 (Omi JN.1), are already enrolled and are ongoing; the second investigational vaccine planned to be evaluated in Cohort 1 has been removed, since the evaluation will be performed in Cohort 3 instead.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Added more recent data for the prevalence of most common SARS-CoV-2 variants in the US.	Prevalence of variants has considerably changed since the writing of protocol amendment 1.	Section 1.1 Synopsis, Section 2.2 Background
Added statements that Omicron KP.2 is the vaccine strain recommended for the 2024-2025 season by the US FDA, if feasible.	To comply with the FDA's recommendation on 13 June 2024.	Section 2.1 Study Rationale, Section 10.9.2.1 Study Rationale
Added a brief summary of the preclinical data on the immunogenicity of KP.2- and JN.1-adapted vaccines presented at the FDA's VRBPAC meeting on 05 June 2024.	To provide a rationale for the clinical evaluation of vaccines targeting SARS-CoV-2 Omicron KP.2 and Omicron JN.1 variants.	Section 2.1 Study Rationale
Updated the clinical overview to add newly reported data.	To provide recent data on Substudy B.	Section 2.2.1 Clinical Overview

Description of Change	Brief Rationale	Section # and Name
Updated text to add Cohort 3 and its analyses to Substudy C.	To evaluate the investigational vaccine targeting the SARS-CoV-2 variant recommended (if feasible) by the US FDA for the 2024-2025 season.	Section 1 Protocol Summary, Section 10.9 Appendix 9: Substudy C [multiple subsections]
Removed the second investigational vaccine planned to be evaluated from Cohort 1.	Timing of the FDA's recommendation for Omicron KP.2 was later than initially anticipated.	Section 1 Protocol Summary, Section 2.1 Study Rationale, Section 10.9 Appendix 9: Substudy C [multiple subsections]
Replaced the term "2024-2025 variant" with the name of the targeted strain.	Global health authorities have recommended a monovalent Omicron JN.1 lineage vaccine (such as JN.1 and KP.2) for the 2024-2025 season, therefore, it is more accurate to refer to the targeted strain.	Section 1.1 Synopsis, Section 4.1 Overall Design, Section 10.9 Appendix 9: Substudy C [multiple subsections]
Removed the Cohort 1 safety and immunogenicity objectives and corresponding updates to statistical analysis sections.	The Cohort 1 safety and immunogenicity objectives were originally planned to allow for evaluation of 2 investigational vaccines, one of which would not be evaluated in Cohort 2. Now, since Cohort 1 includes only 1 vaccine, and this same investigational vaccine will be administered to Cohort 2 participants, its safety and immunogenicity will be evaluated in combination with Cohort 2.	Section 10.9.3 Objectives, Estimands, and Endpoints for Substudy C, Section 10.9.9.3.2 Primary Endpoints/Estimands Analysis, Section 10.9.9.3.3 Exploratory Endpoints Analysis, and Section 10.9.9.4.1 Analysis Timing
Nonsubstantial Modifications		
For Substudy C, added the participant verification process activity, as applicable.	The verification process is performed via a third-party vendor to identify multi-enroller participants in Substudy C and other clinical trials. This process was in place at the start of Substudy C.	Section 10.9.1.3 Schedule of Activities for Substudy C, Section 10.9.8.5.1 Visit C1 – Study Intervention Administration – Day 1
In the SoA for Substudy C, separated the activities of obtaining demography and medical history data into 2 rows.	To align with the Visit C1 study procedures in Section 10.9.8.5.1.	Section 10.9.1.3 Schedule of Activities for Substudy C
For Substudy C, removed "Obtain documentation" from the activity of recording prior COVID-19 vaccines in the CRF.	To align with the Visit C1 study procedures in Section 10.9.8.5.1.	Section 10.9.1.3 Schedule of Activities for Substudy C
For Substudy C, revised text to specify that acute reactions are to be recorded in the CRF (not on the AE page of the CRF) and to equate them with "immediate events".	Substudy C uses a new CRF for reporting of acute reactions. This new CRF identifies acute reactions as "immediate events".	Section 10.9.8.5.1 Visit C1 – Study Intervention Administration – Day 1
For Substudy C, corrected the visit window in the Visit C3 study procedures section heading from 14-16 days to 12-16 days.	To align with the visit window specified in the SoA.	Section 10.9.8.5.3 Visit C3 – 2-Week Follow-Up Visit (12-16 Days After Visit C1) – Cohort 1 and Cohort 3

Description of Change	Brief Rationale	Section # and Name
For Substudy C, replaced "cycle" with "bleeding" in the description of AESI "potential menstrual disturbances"; Added a statement regarding AE/SAE reporting.	To clarify that the additional procedures are to assess participants with disturbances of their normal menstrual bleeding during study participation. To clarify that potential disturbances must be reported as AEs or SAEs, as appropriate	Section 10.9.8.5.12 Additional Procedures for Monitoring of Potential Menstrual Cycle Disturbances
For Substudy C, added the duration for reporting menstrual cycle disturbances.	To clarify that potential menstrual cycle disturbances occurring within 6 months after vaccination are to be reported.	Section 10.9.8.4.1 Adverse Events of Special Interest
Added guidance with respect to study continuation for participants with confirmed pregnancy after receipt of the study intervention.	Section only addressed cases of positive confirmed pregnancy prior to receipt of the study intervention. Study procedures remain unchanged.	Section 8.3.6 Pregnancy Testing
Removed references to Vaccine SAE Report Form.	PSSA is primary route for reporting. Vaccine SAE Report Form is back-up route, mentioned in Section 10.3.4 only.	Multiple subsections within Section 8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting.
Added to Publication Policy section that support on publications may be reportable under the Sunshine Act.	Protocol template requirement.	Section 10.1.11 Publication Policy
Corrected typographical errors and formatting.	Minor corrections.	Throughout

TABLE OF CONTENTS

LIST OF TABLES 14
1. PROTOCOL SUMMARY 15
1.1. Synopsis 15
1.2. Schema 21
1.3. Schedule of Activities 21
2. INTRODUCTION 22
2.1. Study Rationale 22
2.2. Background 24
2.2.1. Clinical Overview 25
2.3. Benefit/Risk Assessment 30
2.4. Risk Assessment 31
2.5. Benefit Assessment 33
2.6. Overall Benefit/Risk Conclusion 33
3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS 33
4. STUDY DESIGN 33
4.1. Overall Design 33
4.2. Scientific Rationale for Study Design 34
4.3. Diversity of Study Population 34
4.4. Choice of Contraception/Barrier Requirements 35
4.5. Justification for Dose 35
4.6. End of Study Definition 35
5. STUDY POPULATION 35
5.1. Inclusion Criteria 36
5.2. Exclusion Criteria 36
5.3. Lifestyle Considerations 36
5.3.1. Contraception 36
5.4. Screen Failures 37
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention 37
6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 37
6.1. Study Intervention(s) Administered 37

6.1.1. Administration 37
6.2. Preparation, Handling, Storage, and Accountability 38
6.2.1. Preparation and Dispensing 39
6.3. Assignment to Study Intervention 39
6.4. Blinding 40
6.5. Study Intervention Compliance 40
6.6. Dose Modification 40
6.7. Continued Access to Study Intervention After the End of the Study 40
6.8. Treatment of Overdose 40
6.9. Prior and Concomitant Therapy 41
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 41
7.1. Discontinuation of Study Intervention 41
7.2. Participant Discontinuation/Withdrawal From the Study 41
7.2.1. Withdrawal of Consent 42
7.3. Lost to Follow-Up 42
8. STUDY ASSESSMENTS AND PROCEDURES 42
8.1. Administrative and Baseline Procedures 43
8.2. Efficacy and/or Immunogenicity Assessments 43
8.2.1. Surveillance for COVID-19 43
8.2.2. Vaccine-Induced Immunogenicity 43
8.2.3. N-Binding Antibody Test 43
8.2.4. Biological Samples 43
8.3. Safety Assessments 44
8.3.1. Physical Examinations 44
8.3.2. Vital Signs 44
8.3.3. Clinical Safety Laboratory Assessments 44
8.3.4. Electronic Diary for Reactogenicity: Substudy A and Substudy B 44
8.3.4.1. Grading Scales: Substudy A and Substudy B 45
8.3.4.2. Local Reactions: Substudy A and Substudy B 45
8.3.4.3. Systemic Events: Substudy A and Substudy B 46
8.3.4.4. Fever: Substudy A and Substudy B 47

8.3.4.5. Antipyretic/Analgesic Medication: Substudy A and Substudy B....48
8.3.5. Electronic Diary for Reactogenicity: Substudy C....48
8.3.5.1. Grading Scales: Substudy C....49
8.3.5.2. Local Reactions: Substudy C....49
8.3.5.3. Systemic Events: Substudy C....50
8.3.5.4. Fever: Substudy C....51
8.3.6. Pregnancy Testing....52
8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting....52
8.4.1. Time Period and Frequency for Collecting AE and SAE Information....52
8.4.1.1. Reporting SAEs to Pfizer Safety....53
8.4.1.2. Recording Nonserious AEs and SAEs on the CRF....53
8.4.2. Method of Detecting AEs and SAEs....54
8.4.3. Follow-Up of AEs and SAEs....54
8.4.4. Regulatory Reporting Requirements for SAEs....54
8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure....55
8.4.5.1. Exposure During Pregnancy....55
8.4.5.2. Exposure During Breastfeeding....56
8.4.5.3. Occupational Exposure....57
8.4.6. Cardiovascular and Death Events....57
8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs....57
8.4.8. Adverse Events of Special Interest....57
8.4.9. Medical Device Deficiencies....58
8.4.10. Vaccination Errors....58
8.5. Pharmacokinetics....59
8.6. Genetics....59
8.6.1. Specified Genetics....59
8.7. Biomarkers....59
8.8. Immunogenicity Assessments....59
8.9. Health Economics....59

8.10. Study Procedures 59
9. STATISTICAL CONSIDERATIONS 59
9.1. Statistical Hypotheses 60
9.2. Analysis Sets 60
9.3. Statistical Analyses 60
9.3.1. General Considerations 61
9.3.1.1. Analysis for Binary Data 61
9.3.1.2. Analysis for Continuous Data 61
9.4. Interim Analyses 62
9.5. Sample Size Determination 62
9.5.1. Immunogenicity Assessment 62
9.5.2. Safety Assessment 62
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 64
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 64
10.1.1. Regulatory and Ethical Considerations 64
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 64
10.1.2. Financial Disclosure 65
10.1.3. Informed Consent/Assent Process 65
10.1.3.1. Informed Consent 65
10.1.3.2. Assent 66
10.1.3.3. Electronic Consent 67
10.1.4. Data Protection 67
10.1.5. Committees Structure 68
10.1.5.1. Data Monitoring Committee 68
10.1.6. Dissemination of Clinical Study Data 68
10.1.7. Data Quality Assurance 70
10.1.8. Source Documents 71
10.1.9. Use of Medical Records 71
10.1.10. Study and Site Start and Closure 72
10.1.11. Publication Policy 73

10.1.12. Sponsor's Medically Qualified Individual....74
10.2. Appendix 2: Clinical Laboratory Tests....75
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting....76
10.3.1. Definition of AE....76
10.3.2. Definition of an SAE....77
10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period....79
10.3.4. Reporting of SAEs....82
10.4. Appendix 4: Contraceptive and Barrier Guidance....84
10.4.1. Male Participant Reproductive Inclusion Criteria....84
10.4.2. Female Participant Reproductive Inclusion Criteria....84
10.4.3. Woman of Childbearing Potential....85
10.4.4. Contraception Methods....86
10.5. Appendix 5: Genetics....88
10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments....89
10.7. Appendix 7: Substudy A....91
10.7.1. Substudy A Summary....91
10.7.1.1. Synopsis....91
10.7.1.2. Schema....91
10.7.1.3. Schedule of Activities for Substudy A....92
10.7.2. Introduction for Substudy A....97
10.7.2.1. Study Rationale....97
10.7.2.2. Background....97
10.7.2.3. Benefits/Risk Assessment....97
10.7.2.4. Benefit Assessment....97
10.7.3. Objectives, Estimands, and Endpoints for Substudy A....97
10.7.4. Study Design for Substudy A....99
10.7.4.1. Overall Study Design....99
10.7.4.2. Scientific Rationale for Substudy A Design....99
10.7.4.3. Rationale for Comparator....100
10.7.4.4. Justification of Dose....100

10.7.4.5. End of Study Definition 100
10.7.5. Study Population for Substudy A 100
10.7.5.1. Inclusion Criteria 100
10.7.5.2. Exclusion Criteria 101
10.7.5.3. Lifestyle Considerations 102
10.7.5.4. Screen Failures 102
10.7.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention 103
10.7.6. Study Interventions and Concomitant Therapy for Substudy A 103
10.7.6.1. Study Intervention Administered 103
10.7.6.2. Preparation, Handling, Storage, and Accountability 104
10.7.6.3. Assignment to Study Intervention 104
10.7.6.4. Blinding 104
10.7.6.5. Study Intervention Compliance 105
10.7.6.6. Dose Modification 105
10.7.6.7. Continued Access to Study Intervention After the End of the Study 105
10.7.6.8. Treatment of Overdose 105
10.7.6.9. Prior and Concomitant Therapy 105
10.7.7. Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal for Substudy A 107
10.7.8. Study Assessments and Procedures for Substudy A 107
10.7.8.1. Administrative Procedures 107
10.7.8.2. Efficacy and Immunogenicity Assessments 109
10.7.8.3. Safety Assessments 112
10.7.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting 114
10.7.8.5. Substudy A Procedures 115
10.7.9. Statistical Considerations for Substudy A 127
10.7.9.1. Statistical Hypotheses 127
10.7.9.2. Analysis Sets 128
10.7.9.3. Statistical Analyses 128

10.7.9.4. Interim Analyses 130
10.7.9.5. Sample Size Determination 130
10.8. Appendix 8: Substudy B 131
10.8.1. Substudy B Summary 131
10.8.1.1. Synopsis 131
10.8.1.2. Schema 131
10.8.1.3. Schedule of Activities for Substudy B 132
10.8.2. Introduction for Substudy B 137
10.8.2.1. Study Rationale 137
10.8.2.2. Background 137
10.8.2.3. Benefits/Risk Assessment 137
10.8.2.4. Benefit Assessment 137
10.8.3. Objectives, Estimands, and Endpoints for Substudy B 137
10.8.4. Study Design for Substudy B 139
10.8.4.1. Overall Study Design 139
10.8.4.2. Scientific Rationale for Substudy B Design 139
10.8.4.3. Rationale for Comparator 140
10.8.4.4. Justification of Dose 140
10.8.4.5. End of Study Definition 140
10.8.5. Study Population for Substudy B 140
10.8.5.1. Inclusion Criteria 140
10.8.5.2. Exclusion Criteria 141
10.8.5.3. Lifestyle Considerations 142
10.8.5.4. Screen Failures 142
10.8.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention 142
10.8.6. Study Interventions and Concomitant Therapy for Substudy B 143
10.8.6.1. Study Intervention Administered 143
10.8.6.2. Preparation, Handling, Storage, and Accountability 144
10.8.6.3. Assignment to Study Intervention 144
10.8.6.4. Blinding 144

10.8.6.5. Study Intervention Compliance....145
10.8.6.6. Dose Modification....145
10.8.6.7. Continued Access to Study Intervention After the End of the Study....145
10.8.6.8. Treatment of Overdose....145
10.8.6.9. Prior and Concomitant Therapy....145
10.8.7. Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal for Substudy B....146
10.8.8. Study Assessments and Procedures for Substudy B....147
10.8.8.1. Administrative Procedures....147
10.8.8.2. Efficacy and Immunogenicity Assessments....148
10.8.8.3. Safety Assessments....152
10.8.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting....153
10.8.8.5. Substudy B Procedures....154
10.8.9. Statistical Considerations for Substudy B....166
10.8.9.1. Statistical Hypotheses....166
10.8.9.2. Analysis Sets....168
10.8.9.3. Statistical Analyses....168
10.8.9.4. Interim Analyses....171
10.8.9.5. Sample Size Determination....171
10.9. Appendix 9: Substudy C....173
10.9.1. Substudy C Summary....173
10.9.1.1. Synopsis....173
10.9.1.2. Schemas....173
10.9.1.3. Schedule of Activities for Substudy C....175
10.9.2. Introduction for Substudy C....181
10.9.2.1. Study Rationale....181
10.9.2.2. Background....181
10.9.2.3. Benefits/Risk Assessment....181
10.9.2.4. Benefit Assessment....181
10.9.3. Objectives, Estimands, and Endpoints for Substudy C....182

10.9.4. Study Design for Substudy C 184
10.9.4.1. Overall Study Design 184
10.9.4.2. Scientific Rationale for Substudy C Design....186
10.9.4.3. Rationale for Comparator....187
10.9.4.4. Justification of Dose....187
10.9.4.5. End of Study Definition 187
10.9.5. Study Population for Substudy C 187
10.9.5.1. Inclusion Criteria....187
10.9.5.2. Exclusion Criteria....188
10.9.5.3. Lifestyle Considerations....189
10.9.5.4. Screen Failures 189
10.9.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention....190
10.9.6. Study Interventions and Concomitant Therapy for Substudy C....190
10.9.6.1. Study Intervention Administered 190
10.9.6.2. Preparation, Handling, Storage, and Accountability....192
10.9.6.3. Assignment to Study Intervention....193
10.9.6.4. Blinding....193
10.9.6.5. Study Intervention Compliance....193
10.9.6.6. Dose Modification....193
10.9.6.7. Continued Access to Study Intervention After the End of the Study....193
10.9.6.8. Treatment of Overdose....194
10.9.6.9. Prior and Concomitant Therapy 194
10.9.7. Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal for Substudy C....195
10.9.8. Study Assessments and Procedures for Substudy C....195
10.9.8.1. Administrative Procedures 195
10.9.8.2. Efficacy and/or Immunogenicity Assessments 197
10.9.8.3. Safety Assessments 201
10.9.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting....202

10.9.8.5. Substudy C Procedures....203
10.9.9. Statistical Considerations for Substudy C....217
10.9.9.1. Statistical Hypotheses....217
10.9.9.2. Analysis Sets....218
10.9.9.3. Statistical Analyses....218
10.9.9.4. Interim Analyses....222
10.9.9.5. Sample Size Determination....222
10.10. Appendix 10: Protocol Amendment History....223
10.11. Appendix 11: Abbreviations....226
11. REFERENCES....230

LIST OF TABLES

Table 1. High-Level Overview of Substudies in Protocol for Variant-Adapted BNT162b2....34
Table 2. Local Reaction Grading Scale: Substudy A and Substudy B....45
Table 3. Systemic Event Grading Scale: Substudy A and Substudy B....46
Table 4. Scale for Fever: Substudy A and Substudy B....48
Table 5. Local Reaction Grading Scale: Substudy C....49
Table 6. Systemic Event Grading Scale: Substudy C....50
Table 7. Scale for Fever: Substudy C....51
Table 8. Probability of Observing at Least 1 AE by Assumed True Event Rate....63
Table 9. Substudy A Design....99
Table 10. Substudy B Design....139
Table 11. Power to Demonstrate Noninferiority Under Different Assumptions of GMR....171
Table 12. Power to Demonstrate Noninferiority Under Different Assumptions of Seroresponse Rate....172
Table 13. Substudy C Design: Cohort 1....185
Table 14. Substudy C Design: Cohort 2....185
Table 15. Substudy C Design: Cohort 3....186

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2/3 Protocol to Investigate the Safety, Tolerability, and Immunogenicity of BNT162b2 RNA-Based Vaccine Candidates for SARS-CoV-2 New Variants in Healthy Individuals

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

Regulatory Agency Identification Number(s):

US IND Number:	19736
EU CT Number:	Not applicable
ClinicalTrials.gov ID:	NCT05997290
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C4591054
Phase:	2/3

Rationale:

BNT162b2 (Comirnaty®) is a ribonucleic acid (RNA)-based vaccine that, has been granted full marketing authorization, conditional marketing authorization, emergency use authorization (EUA), or temporary authorization in a multitude of countries for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The original version of BNT162b2 encodes the ancestral Wuhan-Hu-1 strain spike glycoprotein. In the United States (US), it has been fully licensed for use in individuals 12 years of age and above as of 08 July 2022; EUAs or temporary authorizations are in place for BNT162b2 for those under 12 years of age. In addition, updated bivalent BNT162b2 (original/Omi [B.1.1.529]) versions of the vaccine have received EUAs, full authorization, or temporary authorization. All versions of the vaccine encode the spike protein(s) in nucleoside-modified ribonucleic acid (modRNA) encapsulated in RNA-lipid nanoparticles (LNPs), which has demonstrated potent immunogenicity, high vaccine efficacy (VE), and a favorable safety profile in Phase 1, 2, and 3 human trials, as well as in real-world usage. As of 18 April 2023, the US Food and Drug Administration (FDA) reissued the EUA for the original/Omicron BA.4/BA.5 bivalent messenger ribonucleic acid (mRNA) COVID-19 vaccines to be used for all doses administered to individuals 6 months of age and older. This was also considered an opportunity to simplify the vaccination schedule for most individuals, including that most unvaccinated individuals may receive a single dose of a variant-modified vaccine (rather than 2 doses). The effectiveness of a single dose was supported by observational data from England on the effectiveness of 1 dose of monovalent BNT162b2, and that, among individuals 12 to 17 years of age who had received only 1 dose of BNT162b2, those who had

evidence of previous infection with Alpha, Delta, or Omicron variants had increased protection against symptomatic Omicron infection compared with those who had no evidence of previous infection.

Since the start of the pandemic, a succession of antigenically divergent SARS-CoV-2 lineages have emerged, causing surges in infection rates. Since 2022, the Omicron lineage and many sublineages have caused almost all SARS-CoV-2 infections. With their emergence, they also demonstrated significant escape from established host immunity. The emergence of the BA.2.86 derivative JN.1 lineage and its sublineages over the last year have resulted in the diminished effectiveness of the XBB.1.5 vaccine. Based on weighted estimates in the US, for the 2-week period ending 03 February 2024, JN.1 accounted for 88.9% of all sequenced cases, with XBB.1.5 accounting for an estimated 0.0%. Based on the weighted estimates in the US, for the 2-week period ending 22 June 2024, the variant proportions of all sequenced cases at 5% or higher were: KP.3 at 27.1%, KP.2.3 at 12.3%, KP.2 at 10.7%, JN.1 at 9.2%, LB.1 at 8.6%, and KP.1.1 at 6.3%.

Currently available COVID-19 vaccines continue to provide effective protection against SARS-CoV-2, including substantial protection against hospitalization and death, but reports have suggested potential waning of effectiveness against severe illness several months following vaccination. Considering the expectation that the virus will continue to accumulate mutations and may evolve to more antigenically distant strains in the future, as well as the availability of clinical and real-world evidence indicating that better-matched vaccines improve protection, an update to a COVID-19 vaccine composition that closely matches the most predominant circulating sublineage(s) is justified. This update will improve vaccine-induced immune responses to circulating SARS-CoV-2 sublineages in preparation for annual autumn/winter respiratory virus seasons.

Based on this rationale, Pfizer-BioNTech will evaluate the following vaccine candidate(s):

- BNT162b2 (Omi XBB.1.5) in Substudy A and Substudy B
- BNT162b2 (Omi JN.1) in Substudy C, Cohort 1 and Cohort 2
- BNT162b2 (Omi KP.2) in Substudy C, Cohort 3

Objectives, Endpoints, and Estimands:

Please refer to the substudy appendices for the objectives and endpoints of each substudy.

Overall Design:

This is a Phase 2/3 protocol to investigate the safety, tolerability, and immunogenicity of new BNT162b2 RNA-based vaccine candidates targeting new variants (under monitoring, of interest, and/or of concern) of SARS-CoV-2 in healthy participants. Each substudy design is detailed separately, and these substudies may be conducted in parallel within the framework of this protocol.

High-Level Overview of Substudies in Protocol for Variant-Adapted BNT162b2

Phase	Group/Age	Dose Level	Number of Doses Administered Prior to Enrollment	Days From Last Prior Dose to Study Vax	Number of Doses to Be Administered During Study	Approximate Number of Participants
Substudy A: Evaluation of BNT162b2 (Omi XBB.1.5) in COVID-19 vaccine–experienced participants ≥12 years of age						
2/3	12-55 Yearsa[a]	30 µg	≥3[b]	≥150	1	200
	>55 Years					200
Substudy B: Evaluation of BNT162b2 (Omi XBB.1.5) as a single dose in participants ≥12 years of age who were previously exposed to SARS-CoV-2 and are COVID-19 vaccine naïve						
2/3	≥12 Years	30 µg	0	N/A	1	300
Substudy C – Cohort 1: Evaluation of BNT162b2 (Omi JN.1) as a single dose in participants ≥18 years of age						
2/3	18-55 Years	30 µg	≥0[c]	≥150 (if applicable)	1	25
	>55 Years					25
Substudy C – Cohort 2: Evaluation of BNT162b2 (Omi JN.1) as a single dose in participants ≥12 years of age						
2/3	≥12 Years[a]	30 µg	≥0[c]	≥150 (if applicable)	1	150
Substudy C – Cohort 3: Evaluation of BNT162b2 (Omi KP.2) as a single dose in participants ≥18 years of age						
2/3	18-55 Years	30 µg	≥0[c]	≥150 (if applicable)	1	50
	>55 Years					50

a. A maximum of 20 participants aged 12 through 17 years to be enrolled.
b. Prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5–adapted bivalent vaccine.
c. Participants may be COVID-19 vaccine naïve or experienced, with any number of prior doses of any COVID-19 vaccine.

<u>Substudy A design</u>: BNT162b2 (Omi XBB.1.5) in mRNA COVID-19 vaccine–experienced participants 12 years of age and older

This is an open-label Phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of an updated vaccine against COVID-19. Participants 12 through 55 and >55 years of age who have received at least 3 prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5–adapted bivalent vaccine received at least 150 days prior to study vaccination (Visit A1/Day 1), will receive a single open-label 30-µg dose of BNT162b2 (Omi XBB.1.5). Approximately 400 participants will be enrolled. The study duration will be 6 months, with 5 scheduled visits. COVID-19 surveillance will be conducted throughout the study. A reactogenicity e-diary will be used by participants for 7 days from the day of vaccination. The active collection period for adverse events (AEs) will be through approximately 1 month after vaccination and for serious adverse events

(SAEs) through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 30 participants in each age group who consent to optional additional blood samples will comprise the peripheral blood mononuclear cell (PBMC) subset for exploratory evaluation of B- and T-cell responses and human leukocyte antigen (HLA) typing.

Participants ≥12 years of age from Study C4591044 Cohort 2/Cohort 3 who received bivalent BNT162b2 (wild type [WT]/Omi BA.4/BA.5) 30 µg as a fourth dose will be used as a historical control for immunogenicity.

Substudy B design: **BNT162b2 (Omi XBB.1.5) as a single dose in participants ≥12 years of age who were previously exposed to SARS-CoV-2 and are COVID-19 vaccine naïve**

This is an open-label Phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of an updated vaccine against COVID-19. Participants ≥12 years of age who were previously exposed to SARS-CoV-2 and are COVID-19 vaccine naïve will receive a single 30-µg dose of BNT162b2 (Omi XBB.1.5) (open-label). Approximately 300 participants will be enrolled. The study duration will be 6 months, with 5 scheduled visits. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 30 participants aged ≥18 years who consent to collection of optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing.

Participants from C4591054 Substudy A who received BNT162b2 (Omi XBB.1.5) 30 µg will be used as a control group for immunogenicity.

Substudy C design: **BNT162b2 (Omi JN.1) and BNT162b2 (Omi KP.2) as a single dose in participants ≥12 years of age**

This is a Phase 2/3 open-label study to evaluate the safety, tolerability, and immunogenicity of 2 BNT162b2-based vaccines, each targeting a predominant circulating variant of SARS-CoV-2. The substudy will be divided into 3 cohorts.

Cohort 1 will enroll approximately 50 participants 18 years of age and older (approximately 25 participants each in 18 through 55 and >55 years of age groups), who will receive a single 30-µg dose of BNT162b2 (Omi JN.1). The study duration will be approximately 6 months, with 6 scheduled visits. Reactogenicity e-diaries will be used to collect prespecified local reaction and systemic event data during the 7-day collection period, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution). The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity.

Cohort 2 will enroll participants ≥12 years of age who will receive a single open-label 30-µg dose of BNT162b2 (Omi JN.1). Enrollment into Cohort 2 will begin once Cohort 1 has completed enrollment. Approximately 150 participants will be enrolled into Cohort 2, resulting in a total of 200 participants receiving BNT162b2 (Omi JN.1) (including the 50 participants from Cohort 1). The study duration will be approximately 6 months, with 5 scheduled visits (no 2-week visit). Reactogenicity e-diaries will be used to collect prespecified local reaction and systemic event data during the 7-day collection period, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution). The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 30 participants each in the 18- through 55-year and >55-year age groups who consent to collection of optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing.

For both cohorts, participants from C4591054 Substudy A who received BNT162b2 (Omi XBB.1.5) 30 µg will be used as a control group for immunogenicity assessment (for the matched time points).

Cohort 3 will enroll participants ≥18 years of age who will receive a single open-label 30-µg dose of BNT162b2 (Omi KP.2), which targets the SARS-CoV-2 variant Omicron KP.2. Approximately 100 participants will be enrolled. The study duration will be approximately 6 months, with 6 scheduled visits. Reactogenicity e-diaries will be used to collect prespecified local reaction and systemic event data during the 7-day collection period, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution). The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 20 participants each in the 18- through 55-year and >55-year age groups who consent to collection of optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing.

Participants from Cohorts 1 and 2 of Study C4591054 – Substudy C who received BNT162b2 (Omi JN.1) 30 µg will be used as a control group for the immunogenicity assessment of BNT162b2 (Omi KP.2).

All cohorts will enroll participants who are either COVID-19 vaccine naïve or experienced. Those who have received prior COVID-19 vaccine(s) must have received the most recent dose at least 150 days prior to study vaccination (Visit C1/Day 1).

Number of Participants:

Substudy A: Approximately 400 participants will be enrolled.

Substudy B: Approximately 300 participants will be enrolled.

Substudy C:

- Cohort 1: Approximately 50 participants will be enrolled.
- Cohort 2: Approximately 150 participants will be enrolled.
- Cohort 3: Approximately 100 participants will be enrolled.

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

Study Population:

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

Study Arms and Duration:

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

Statistical Methods:

Statistical methods applicable to all substudies are specified in the body of the protocol. Statistical methods specific to each substudy are specified in the respective substudy appendix.

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 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 clinical development of variant-adapted BNT162b2 vaccines. 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 variant-adapted BNT162b2 vaccines 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.
- The study procedure–related risks include:
    - Venipuncture will be performed during the study.
    - Participants will be expected to commit time and may experience some discomfort while undergoing study assessments.

1.2. Schema

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

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 illness visit is required at any time between Visit 1 (vaccination) and approximately 6 months after the participant's study vaccination when COVID-19/MIS-C 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 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness rather than vaccine reactogenicity. For details for Substudy A, see Section 10.7.8.5.7, for Substudy B, see Section 10.8.8.5.7, and for Substudy C, see Section 10.9.8.5.8.

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.

Refer to the SoA for Substudy A in Section 10.7.1.3, Substudy B in Section 10.8.1.3, and Substudy C in Section 10.9.1.3.

2. INTRODUCTION

BNT162b2 (Comirnaty®) is an RNA-based vaccine that, as of May 2023, has been granted full marketing authorization, conditional marketing authorization, EUA, or temporary authorization in a multitude of countries for the prevention of COVID-19 caused by SARS-CoV-2. The original version of BNT162b2 encodes the ancestral Wuhan-Hu-1 strain spike glycoprotein.[1,2] In the US, it has been fully licensed for use in individuals 12 years of age and above as of 08 July 2022[3]; EUAs or temporary authorizations are in place for BNT162b2 for those under 12 years of age.[4] In addition, updated bivalent BNT162b2 (original/Omi [B.1.1.529])[5] versions of the vaccine have received EUAs, full authorization, or temporary authorization.[5,6,7] Finally, as of 18 April 2023, the FDA reissued the EUA for the original/Omicron BA.4/BA.5 bivalent mRNA COVID-19 vaccines to be used for all doses administered to individuals 6 months of age and older. This was also considered an opportunity to simplify the vaccination schedule for most individuals, including that most unvaccinated individuals may receive a single dose of a variant-modified vaccine (rather than 2 doses). The effectiveness of a single dose was supported by observational data from England on the effectiveness of 1 dose of monovalent BNT162b2, and that, among individuals 12 to 17 years of age who had received only 1 dose of BNT162b2, those who had evidence of previous infection with Alpha, Delta, or Omicron variants had increased protection against symptomatic Omicron infection compared with those who had no evidence of previous infection.[8]

All versions of the vaccine encode the spike protein(s) in modRNA encapsulated in RNA-LNPs, which has demonstrated potent immunogenicity, high VE, and a favorable safety profile in Phase 1, 2, and 3 human trials,[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 RNA-based COVID-19 vaccines to further protect against COVID-19 caused by emergent and potentially more antigenically diverse variants.

2.1. Study Rationale

This protocol allows for the rapid initiation of clinical studies to evaluate the safety, tolerability, and immunogenicity of BNT162b2-based vaccines adapted to emerging variants (under monitoring, of interest, and/or of concern).

Since the start of the pandemic, a succession of antigenically divergent SARS-CoV-2 lineages have emerged, causing surges in infection rates. Since 2022, the Omicron lineage and its many sublineages have caused almost all SARS-CoV-2 infections. With their emergence, they also demonstrated significant escape from established host immunity.[12] The emergence of the BA.2.86 derivative JN.1 lineage and sublineages over the last year have resulted in the diminished effectiveness of the XBB.1.5 vaccine. Based on weighted estimates in the US, for the 2-week period ending 03 February 2024, JN.1 accounted for 88.9% of all sequenced cases, with XBB.1.5 accounting for an estimated 0.0%. Based on the weighted estimates in the US for the 2-week period ending 22 June 2024,

the variant proportions of all sequenced cases at 5% or higher were: KP.3 at 27.1%, KP.2.3 at 12.3%, KP.2 at 10.7%, JN.1 at 9.2%, LB.1 at 8.6%, and KP.1.1 at 6.3%.[13]

Currently available COVID-19 vaccines continue to provide effective protection against SARS-CoV-2,[12,14,15,16,17,18] including substantial protection against hospitalization and death, but reports have suggested potential waning of effectiveness against severe illness several months following vaccination.[18,19,20] Considering the expectation that the virus will continue to accumulate mutations and may evolve to more antigenically distant strains in the future, as well as the availability of clinical and real-world evidence indicating that better-matched vaccines improve protection,[21] an update to a COVID-19 vaccine composition that closely matches the most predominant circulating sublineage(s) is justified. This update will improve vaccine -induced immune responses to circulating SARS-CoV-2 sublineages in preparation for annual autumn/winter respiratory virus seasons.

Substudy A (Section 10.7) and Substudy B (Section 10.8) will evaluate the safety, tolerability, and immunogenicity of BNT162b2 (Omi XBB.1.5), each in a different population. This variant was selected based on the WHO statement on the antigen composition of COVID-19 vaccines, issued on 18 May 2023, recommending use of a monovalent XBB.1 descendent lineage, such as XBB.1.5, as the vaccine antigen[12] (and recommendation to retain this strain on 13 December 2023[22]). The EMA had released similar guidance on 06 June 2023 recommending that a monovalent vaccine targeting the XBB.1 descendent lineages be administered beginning in autumn 2023.[23] The FDA's VRBPAC on 15 June 2023 recommended that updated COVID-19 vaccines target the XBB.1.5 Omicron subvariant as a monovalent vaccine.[24]

A new SARS-CoV-2 variant, JN.1, globally overtook the previously circulating XBB family of variants between December 2023 and January 2024.[25] By 25 May 2024, in the US, the JN.1 sublineage, KP.2, was among the lineages with the highest prevalence, 14.8% of weighted sequenced cases.[13] In April 2024, the EMA and WHO recommended the use of a monovalent JN.1 lineage antigen for the 2024-2025 variant-adapted vaccine.[25,26] The EMA confirmed its recommendation again on 19 July 2024.[27] On 05 June 2024, the FDA's VRBPAC advised that updated COVID-19 vaccines target the JN.1 Omicron strain as a monovalent vaccine, with the FDA’s agreement to this recommendation on 06 June 2024. On 13 June 2024, the FDA changed its recommendation for updated mRNA vaccines to target the Omicron KP.2 strain, if feasible.[28]

Substudy C (Section 10.9) will evaluate the safety, tolerability, and immunogenicity of BNT162b2 (Omi JN.1) in Cohorts 1 and 2 and BNT162b2 (Omi KP.2) in Cohort 3.

Preclinical data in mice, presented at the VRBPAC meeting on 05 June 2024, show that, similar to a JN.1-adapted vaccine, a KP.2-adapted vaccine elicits improved neutralizing responses against a broad panel of JN.1 sublineage pseudoviruses as compared to the XBB.1.5 vaccine. There also appeared to be a trend toward higher responses elicited by the KP.2 vaccine compared to the JN.1 vaccine against some sublineages, although the translation of those trends into magnitude of clinical differences is not defined.[29,30]

2.2. Background

SARS-CoV-2, a novel β-coronavirus, is a highly transmissible and pathogenic respiratory virus responsible for the COVID-19 pandemic. Studies of SARS-CoV-2 and SARS-CoV-1, a closely related coronavirus that caused the 2003 SARS outbreak, demonstrated that effective antibody protection could be achieved through spike-specific antibodies.[31,32] Therefore, vaccines targeting the spike protein of SARS-CoV-2 have been used as a critical mitigation strategy of the COVID-19 pandemic. Mutations resulting in the development of new variants may, however, reduce the efficacy of vaccines against specific strains.

The SARS-CoV-2 epidemiological landscape has been dominated by successive cycles of emergent Omicron sublineages since late 2021. XBB.1.5 had been dominant globally since February 2023; other XBB sublineages (eg, XBB.1.16, XBB.1.9.1, EG.5) continued to increase in prevalence thereafter, until the emergence and rapid predominance of JN.1 globally by January 2024[33,34] and dominance of KP.2 by late May 2024.[13]

By the fourth quarter of 2022 (October-December), the majority of the US population had evidence of exposure to SARS-CoV-2, from vaccination or infection or both. A 2022 nationwide blood donor seroprevalence study in individuals aged ≥16 years, conducted by the CDC, of COVID-19 infection– and vaccination-induced antibody seroprevalence showed that, for the 3-month period of October-December 2022, 96.7% (95% CI: 93.9%, 98.3%) of the US study-wide population were seropositive, with 77.5% (95% CI: 75.1%, 79.8%) being infection-induced.[35] An earlier study demonstrated that the greatest increases in seroprevalence during September 2021 to February 2022 occurred in age groups with the lowest vaccination coverage.[36] It can therefore be anticipated that the majority of unvaccinated individuals are likely to have been exposed to SARS-CoV-2 and have some level of natural immunological responses. Thus, as would be expected after natural exposure, in all studies where immune response has been evaluated based on prior SARS-CoV-2 exposure, responses in individuals who have previously been exposed to SARS-CoV-2 are greater than responses in those who have not.

In the present epidemiological setting of high population seropositivity, early evidence indicates that updated monovalent XBB.1.5-derived COVID-19 vaccines provide protection against symptomatic SARS-CoV-2 infection with JN.1 and XBB-related circulating lineages, though to different degrees. A CDC study of immunocompetent adults aged ≥18 years reported an early estimate for updated 2023-2024 XBB.1.5-adapted vaccine effectiveness against symptomatic infection (compared to no receipt) of 54% (95% CI: 46%, 60%) at a median (IQR) of 52 (29, 75) days after receipt. Further, based on SGT presence or failure, as an indicator of likely non-JN.1 and likely JN.1 infections, respectively, the CDC reported effectiveness against symptomatic illness of 60% (95% CI: 35%, 75%) for infections likely not related to JN.1 and 49% (95% CI: 19%, 68%) for infections likely related to JN.1.[37]

Although the early available data indicate that XBB.1.5-adapted vaccines provide effective real-world protection against JN.1,[37] neutralization studies have demonstrated that JN.1 exhibits increased immune evasion from both infection-induced and vaccine-induced immunity compared with earlier virus strains.[38,39] Consistent with laboratory investigations,

an epidemiological study conducted by the Statens Serum Institut recently reported that BA.2.86 and, in particular, the JN.1 sublineage were less sensitive to vaccine-induced immune protection acquired from vaccination with XBB.1.5-adapted vaccine by a factor of more than 1.5-fold compared to non–BA.2.86-related variants with respect to the odds of SARS-CoV-2 infection.[40] A second epidemiological study conducted by the Netherlands National Institute for Public Health and Environment has also reported early evidence indicating immune escape of BA.2.86/JN.1 (compared to XBB) from XBB.1.5 vaccination and recent prior infection among adults aged 18 through 85 years (odds ratio [OR] = 1.6 [95% CI: 0.9, 2.9] and OR = 2.6 [95% CI: 1.1, 6.3], respectively).[41]

These data continue to reinforce that continual virus evolution toward improved viral fitness, immune escape, and transmission is impacting VE over time.[42] Vaccine-induced immunity will likely be further reduced over time, consistent with waning VE that has been observed after original monovalent and bivalent COVID-19 vaccination,[37] and as viral evolution continues to cause divergence between the antigen composition of COVID-19 vaccines and circulating SARS-CoV-2 strains.

Vaccines remain effective in preventing severe illness, though their efficacy against KP.2 is expected to be reduced, as has been demonstrated against its parental lineage, JN.1. Updated vaccines, therefore, are necessary for more relevant variant-adapted immunity. Preclinical studies show that JN.1- and KP.2-adapted vaccines elicit improved responses against a broad panel of JN.1 sublineages as compared to the XBB.1.5-adapted vaccine, also providing support for a vaccine update in line with regulatory agency recommendations.[25,26,28]

2.2.1. Clinical Overview

Study C4591001 (NCT04368728) was a Phase 1/2/3 trial in ~46,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from the RNA-based BNT162b2 vaccine candidate.[43] The trial was conducted in a heterogeneous study population: eligible participants ≥12 years of age who were healthy, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants.

Available immunogenicity data from Phase 1 participants showed that BNT162b2 induced a robust IgG-binding response to S1 and a SARS-CoV-2–neutralizing response. Immunogenicity substantially increased following the second dose of vaccine. BNT162b2 induces a strong antigen-specific Th1-skewed CD4+ response and a strong antigen-specific CD8+ response. In a mid–November 2020 analysis of 36,621 participants randomized 1:1 to vaccine or placebo, 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.[44]

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.[45] Furthermore, from the same analysis, BNT162b2 was shown to have an efficacy of:

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

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

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.[46]

During the development of BNT162b2, data were not collected to specifically evaluate the vaccine as a single dose in unvaccinated individuals. Study C4591001 was initiated early in the pandemic when the overall natural population COVID-19 exposure was low. Consequently, the Phase 1 evaluation of BNT162b2 in SARS-CoV-2–naïve individuals in Study C4591001 demonstrated that neutralizing antibody titers after Dose 1, just prior to Dose 2, were limited.[47]

In the Phase 2 evaluation of BNT162b2 in Study C4591001, although known prior exposure to SARS-CoV-2 was exclusionary, a few individuals (who had presumably had asymptomatic infection) were included. Among 175 participants who received BNT162b2 (30 µg) in the all-available immunogenicity population and had data 1 month after Dose 2, 5 were baseline SARS-CoV-2 positive. The post–Dose 2 geometric mean neutralizing antibody titer in these 5 individuals was 2585.9 (95% CI: 737.7, 9064.8), compared to 300.4 (95% CI: 264.8, 340.8) in the 170 individuals who were baseline negative.

In the Phase 3 C4591031 (NCT04955626) Substudy A, approximately 10,000 participants who had previously received 2 doses of BNT162b2 as a primary series in Study C4591001 were randomized 1:1 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. In a per-protocol interim safety and efficacy analysis conducted in October 2021, symptomatic COVID-19 occurrence was measured from ≥7 days after the booster dose 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.[48]

The Phase 3 C4591031 (NCT04955626) Substudy D evaluated additional doses of BNT162b2 in healthy individuals previously vaccinated with BNT162b2. It was designed to assess an Omicron-specific vaccine, BNT162b2 Omicron, a monovalent BNT162b2 RNA-LNP vaccine utilizing modified RNA and encoding the P2 S containing Omicron variant–specific mutations (B.1.1.529 sublineage BA.1). This study is clinically complete, with the final data analysis pending. Interim data analysis demonstrated that overall, the reactogenicity profile (local reactions, systemic events) within 7 days after 30 µg BNT162b2 Omicron and BNT162b2 administered as a third or fourth dose was similar to that previously observed after a third dose of BNT162b2. In participants without prior evidence of infection up to 1 month after Dose 4, the ratio of GMTs for the BNT162b2 Omicron group to the BNT162b2 group (GMR) was 1.75 (2-sided 95% CI: 1.39, 2.22). As the lower bound of the 2-sided 95% CI for GMR was >1, the simple superiority of BNT162b2 Omicron to BNT162b2 was achieved. There was a substantial increase in SARS-CoV-2 50% neutralizing GMTs for the Omicron (BA.1) variant and reference strains at the 1-month post–Dose 4 time point compared to the prevaccination baseline. Per the descriptive immunogenicity analysis of the Omicron variant and reference strains for both vaccine groups, the immune responses up to 1 month after Dose 4 (GMTs, GMFRs, seroresponse rates) were generally higher for participants with baseline positive SARS-CoV-2 status compared to those with baseline negative status.

C4591031 Substudy E was a Phase 3 trial in approximately 2900 participants 18 years of age and older who have previously received 3 doses of BNT162b2 (30-µg dose). Participants in this substudy received a fourth dose of either BNT162b2 or BNT162b2 Omicron (BA.1 sublineage) or a combination of both at a total dose level of either 30 µg or 60 µg. From the available safety data from this study, the tolerability and safety profile of bivalent BNT162b2 30 µg, bivalent BNT162b2 60 µg, and monovalent BNT162b2 60 µg up to 1 month after study vaccination (to the data cutoff date) was acceptable and consistent with the known safety profile of BNT162b2 and previously reported AE profile for Omicron BA.1–modified BNT162b2 vaccines. In participants >18 through 55 years of age,

monovalent and bivalent Omicron-modified vaccines at the 30-µg dose level showed a similar local reaction and systemic event profile as the prototype BNT162b2 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 reactogenicity with the 30-µg dose level. From the immunogenicity data, in participants >55 years of age without evidence of COVID-19 infection, Omicron BA.1 neutralization activity substantially increased with Omicron-modified bivalent vaccines as a fourth dose. Additionally, analysis of immunogenicity data from this study demonstrated a robust Omicron BA.1 and reference-strain vaccine-elicited immune response to both monovalent and bivalent Omicron BA.1–modified vaccines when administered as a fourth dose to BNT162b2-experienced participants 18 through 55 years of age.

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

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

Study C4591054 – Substudy A enrolled participants who had received at least 3 prior doses of mRNA COVID-19 vaccines, with the last dose being an Omicron BA.4/5 vaccine at least 150 days prior to study vaccination. Participants were administered a single 30-µg dose of BNT162b2 (Omi XBB.1.5). In the recently published article on this study[49] (NCT05997290), the SARS-CoV-2 FFRNT 50% neutralizing titers against Omicron XBB.1.5, EG.5.1, and

BA.2.86 were increased 7 days after vaccination with the XBB.1.5-adapted BNT162b2 compared with baseline levels, and were numerically higher than those in the matched comparator group of participants who had received the BA.4/BA.5-adapted BNT162b2 (figure s1 in the article). The SARS-CoV-2 FFRNT 50% neutralizing titers against Omicron XBB.1.5, EG.5.1, and BA.2.86 were further increased 1 month after vaccination with the XBB.1.5-adapted BNT162b2 compared with baseline levels. GMTs at 1 month were similar for all 3 sublineages (GMT range overall, 452.5-561.3). Baseline GMTs were higher for Omicron BA.2.86 compared with XBB.1.5 and EG.5.1; GMFRs from baseline to 1 month after vaccination were similar for XBB.1.5 (overall GMFR, 7.0 [95% CI, 4.3, 11.4]) and EG.5.1 (8.7 [5.4, 14.1]) and slightly lower for BA.2.86 (4.5 [3.1, 6.5]). Postvaccination titers were generally higher in participants >55 years of age (GMT range, 559.3-732.3) compared with those from 18 through 55 years of age (370.3-444.4), while the baseline titers were generally similar in the 2 age groups.

Seven days after vaccination, the overall percentage of participants with seroresponse was numerically higher after the XBB.1.5-adapted BNT162b2 (overall range, 45.0%-62.5%) than after the BA.4/BA.5-adapted BNT162b2 (17.5%-25.0%). One month after vaccination with the XBB.1.5-adapted BNT162b2, the percentages of participants overall with a seroresponse to Omicron XBB.1.5 and EG.5.1 were similar (67.6% and 73.0%, respectively) and slightly higher than the seroresponse to BA.2.86 (59.5%). The percentages of participants with a seroresponse to Omicron XBB.1.5 were similar in 18- through 55-year-old and >55-year-old participants (68.4% and 66.7%, respectively). The percentages of participants with a seroresponse to Omicron EG.5.1 and BA.2.86 were slightly lower for 18- through 55-year-olds (68.4% and 52.6%, respectively) than for >55-year-olds (77.8% and 66.7%).

Study C4591054 – Substudy B enrolled participants who were naïve to COVID-19 vaccines and who had at least 1 positive test result for SARS-CoV-2 more than 28 days before study vaccination. The study demonstrated noninferiority of the immune response against Omicron XBB.1.5 after a single dose of BNT162b2 (Omi XBB.1.5) in Substudy B COVID-l19 vaccine–naïve participants compared to Substudy A COVID-19 vaccine–experienced participants at 1 month after vaccination. Neutralizing titers against Omicron XBB.1.5 substantially increased 1 month after study vaccination in all age groups. GMTs, GMFRs, and the percentage of participants achieving seroresponse were higher in vaccine-naïve participants compared to vaccine-experienced participants. The observed immune responses as reflected by GMFRs were also higher in vaccine-naïve baseline SARS-CoV-2 positive participants than vaccine-experienced baseline SARS-CoV-2 positive participants.

These data support administration of the XBB.1.5-adapted BNT162b2 in vaccine-experienced and vaccine-naïve individuals ≥12 years of age. Safe and effective variant-adapted COVID-19 vaccines closely matched to circulating strains will likely remain critical to protect the vulnerable against serious COVID-19 outcomes and to reduce the burden on healthcare systems.

2.3. Benefit/Risk Assessment

As a result of the global COVID-19 pandemic, several licensed SARS-CoV-2 vaccines are 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 the BNT162 family of 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.[50,51]

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

2.4. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Interventions: BNT162b2 original and all variant-adapted versions		
For BNT162b2: Key identified risks for BNT162b2 include 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 key risks identified for BNT162b2 are lymphadenopathy; hypersensitivity reactions, such as rash, pruritus, urticaria, angioedema, and anaphylaxis; and myocarditis and pericarditis. For all variant-adapted versions of BNT162b2: These vaccines have the same modRNA platforms (with sequence changes that are variant specific) and LNP formulation as BNT162b2; therefore, the safety profiles are expected to be similar to that of BNT162b2.	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.[44] 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 a primary series in children ages 5 through <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 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 Study C4591001 and has resulted in identification of some additional adverse reactions (risks) as noted in the SRSD.	Local reactions and systemic events will be recorded using a reactogenicity e-diary to monitor local reactions and systemic events in real time. Collection of AEs from signing of the ICD through 1 month and SAEs through 6 months after study vaccination. EDMC review throughout the study to review all safety data. Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in the procedure section of the substudy appendices.

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

2.5. Benefit Assessment

Benefits to individual participants enrolled in each substudy:

- The opportunity to receive a dose of a potentially efficacious COVID-19 vaccine that may convey better protection against a SARS-CoV-2 variant.
- Contributing to research to help others.

2.6. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risks to participants in each substudy, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccines are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

For substudy-specific objectives and endpoints, refer to each respective substudy appendix.

For Substudy A, refer to Section 10.7.3, for Substudy B, refer to Section 10.8.3, and for Substudy C, refer to Section 10.9.3.

4. STUDY DESIGN

4.1. Overall Design

This study protocol is divided into substudies to investigate the safety, tolerability, and immunogenicity of 1 or more SARS-CoV-2 variant-adapted BNT162b2 vaccine candidates. Each substudy design is detailed separately in the respective substudy appendix. Substudies (see Table 1) may be conducted in parallel within the framework of this protocol. For more details on study designs, refer to the appendix of each substudy: Substudy A (Section 10.7), Substudy B (Section 10.8), and Substudy C (Section 10.9).

Table 1. High-Level Overview of Substudies in Protocol for Variant-Adapted BNT162b2

Phase	Group/Age	Dose Level	Number of Doses Administered Prior to Enrollment	Days From Last Prior Dose to Study Vax	Number of Doses to Be Administered During Study	Approximate Number of Participants
Substudy A: Evaluation of BNT162b2 (Omi XBB.1.5) in COVID-19 vaccine–experienced participants ≥12 years of age						
2/3	12-55 Years[a]	30 µg	≥3[b]	≥150	1	200
	>55 Years					200
Substudy B: Evaluation of BNT162b2 (Omi XBB.1.5) as a single dose in participants ≥12 years of age who were previously exposed to SARS-CoV-2 and are COVID-19 vaccine naïve						
2/3	≥12 Years	30 µg	0	N/A	1	300
Substudy C – Cohort 1: Evaluation of BNT162b2 (Omi JN.1) as a single dose in participants ≥18 years of age						
2/3	18-55 Years	30 µg	≥0[c]	≥150 (if applicable)	1	25
	>55 Years					25
Substudy C – Cohort 2: Evaluation of BNT162b2 (Omi JN.1) as a single dose in participants ≥12 years of age						
2/3	≥12 Years[a]	30 µg	≥0[c]	≥150 (if applicable)	1	150
Substudy C – Cohort 3: Evaluation of BNT162b2 (Omi KP.2) as a single dose in participants ≥18 years of age						
2/3	18-55 Years	30 µg	≥0[c]	≥150 (if applicable)	1	50
	>55 Years					50

a. A maximum of 20 participants aged 12 through 17 years to be enrolled.
b. Prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5–adapted bivalent vaccine.
c. Participants may be COVID-19 vaccine naïve or experienced, with any number of prior doses of any COVID-19 vaccine.

4.2. Scientific Rationale for Study Design

Refer to Section 2.1 for the protocol study rationale.

See the substudy appendices for the rationales supporting each substudy.

4.3. Diversity of Study Population

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

For smaller studies, there may be less representation with respect to race, ethnicity, and geographic location.

4.4. Choice of Contraception/Barrier Requirements

BNT162b2 is approved for use without any contraceptive precautions. All study interventions 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.

4.5. Justification for Dose

The 30-µg dose level of BNT162b2 was shown to be effective and has been approved in multiple countries worldwide in both the original and bivalent formulations. Refer to the applicable substudy appendix for justification of doses other than 30 µg.

4.6. End of Study Definition

The end of each substudy is defined as the date of the last visit of the last participant in the substudy. A participant is considered to have completed the substudy if he/she has completed all phases of the substudy, including the last visit.

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

Each substudy will be analyzed, reported, and disclosed separately.

5. STUDY POPULATION

Each substudy 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 inclusion criteria are met.

See Section 10.7.5.1 for the Substudy A inclusion criteria.

See Section 10.8.5.1 for the Substudy B inclusion criteria.

See Section 10.9.5.1 for the Substudy C inclusion criteria.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the exclusion criteria apply.

See Section 10.7.5.2 for Substudy A exclusion criteria.

See Section 10.8.5.2 for the Substudy B exclusion criteria.

See Section 10.9.5.2 for the Substudy C exclusion criteria.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention administration, if applicable.

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

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

5.4. Screen Failures

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

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

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

For Substudy A, refer to Section 10.7.5.5.

For Substudy B, refer to Section 10.8.5.5.

For Substudy C, refer to Section 10.9.5.5.

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.

Refer to the substudy appendices for the variant-adapted BNT162b2 vaccine used in each substudy.

6.1. Study Intervention(s) Administered

For Substudy A, refer to Section 10.7.6.1.

For Substudy B, refer to Section 10.8.6.1.

For Substudy C, refer to Section 10.9.6.1.

6.1.1. Administration

Participants will receive study intervention as allocated by the IRT in accordance with the substudy's SoA.

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

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

Study intervention administration details will be recorded on the CRF.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

Study intervention will be provided in either single-dose or multidose vials. If multidose vials are provided, they are intended for single use, as outlined in the IPM.

6.3. Assignment to Study Intervention

Allocation (randomization) of participants to vaccine groups, if applicable to the substudy, will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned 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.

Study intervention will be dispensed at the study visits summarized in the substudy 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

Blinding arrangements for participants, site personnel, and the sponsor are detailed in the substudy appendices.

Refer to Section 10.7.6.4 for Substudy A.

Refer to Section 10.8.6.4 for Substudy B.

Refer to Section 10.9.6.4 for Substudy C.

6.5. Study Intervention Compliance

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

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.

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

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

6.8. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

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

Refer to Section 10.7.6.9 for Substudy A.

Refer to Section 10.8.6.9 for Substudy B.

Refer to Section 10.9.6.9 for Substudy C.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

This is a protocol of single-dose substudies; therefore, this section is not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up;
- Death;
- Study terminated by Pfizer;
- Reactogenicity event (from Substudy C onwards);
- AEs;
- Participant 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 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 specifically withdraws consent or assent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from 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/participate in telehealth communication for a required study visit:

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

See Section 10.7.8 for assessments and procedures specific to Substudy A.

See Section 10.8.8 for assessments and procedures specific to Substudy B.

See Section 10.9.8 for assessments and procedures specific to Substudy C.

8.1. Administrative and Baseline Procedures

For Substudy A, refer to Section 10.7.8.1.

For Substudy B, refer to Section 10.8.8.1.

For Substudy C, refer to Section 10.9.8.1.

8.2. Efficacy and/or Immunogenicity Assessments

For Substudy A, refer to Section 10.7.8.2.

For Substudy B, refer to Section 10.8.8.2.

For Substudy C, refer to Section 10.9.8.2.

8.2.1. Surveillance for COVID-19

Refer to the appendix of each substudy.

8.2.2. Vaccine-Induced Immunogenicity

Refer to the appendix of each substudy.

8.2.3. N-Binding Antibody Test

Refer to the appendix of each substudy.

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

The participant may request that their samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing, if included in a particular substudy.

For blood sampling details, refer to the appendix of each substudy.

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.

For Substudy A, refer to Section 10.7.8.3.

For Substudy B, refer to Section 10.8.8.3.

For Substudy C, refer to Section 10.9.8.3.

8.3.1. Physical Examinations

Refer to the appendix of each substudy.

8.3.2. Vital Signs

Refer to the appendix of each substudy.

8.3.3. Clinical Safety Laboratory Assessments

Refer to the appendix of each substudy.

8.3.4. Electronic Diary for Reactogenicity: Substudy A and Substudy B

Participants 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. All participants 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. 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 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 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: Substudy A and Substudy B

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.[52]

8.3.4.2. Local Reactions: Substudy A and Substudy B

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

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 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

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 and report it in the designated CRF as Grade 4. A Grade 4 reaction will also be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

Table 2. Local Reaction Grading Scale: Substudy A and Substudy B

	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

Table 2. Local Reaction Grading Scale: Substudy A and Substudy B

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

8.3.4.3. Systemic Events: Substudy A and Substudy B

During the reactogenicity e-diary reporting period, participants 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 3.

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 and report it in the designated CRF as Grade 4. A Grade 4 systemic event will also be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

Table 3. Systemic Event Grading Scale: Substudy A and Substudy B

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

Table 3. Systemic Event Grading Scale: Substudy A and Substudy B

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

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

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with prespecified 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 Section 10.7.8.5.7 and Section 10.7.8.5.8 for Substudy A, and Section 10.8.8.5.7 and Section 10.8.8.5.8 for Substudy B).

8.3.4.4. Fever: Substudy A and Substudy B

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature 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 during analysis according to the scale shown in Table 4.

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 and report it in the designated CRF as fever >40.0°C (>104.0°F). Fevers >40.0°C (>104.0°F) will also be collected as an AE on the CRF and assessed by the investigator using the AE intensity grading scale (Section 10.3.3).

Table 4. Scale for Fever: Substudy A and Substudy B

≥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: Substudy A and Substudy B

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. Electronic Diary for Reactogenicity: Substudy C

Participants 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. All participants will be asked to monitor and record prespecified local reactions and systemic events in an e-diary during the 7-day collection period, or longer for ongoing symptoms, from the day of administration of the study intervention (Day 1). The reactogenicity e-diary allows recording of these assessments each day, thus providing the accurate representation of the participant's experience. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians, at all times, via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. If a participant withdraws because of prespecified event(s) recorded in the e-diary, the event(s) should be recorded in the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

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

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

8.3.5.1. Grading Scales: Substudy C

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.[52]

8.3.5.2. Local Reactions: Substudy C

Following vaccination (where Day 1 is the day of vaccination), participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the 7-day e-diary collection period, the participant will be requested to report that information and/or any new events that develop to the investigator or the study staff.

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 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, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify Pfizer. A Grade 4 reaction will be collected on the CRF.

Table 5. Local Reaction Grading Scale: Substudy C

	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 local reaction as Grade 4.

8.3.5.3. Systemic Events: Substudy C

Following vaccination (where Day 1 is the day of vaccination), participants 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. If a systemic event persists beyond the end of the 7-day e-diary collection period, the participant will be requested to report that information and/or any new events that develop to the investigator or study staff.

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 events as Grade 4 after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify Pfizer. A Grade 4 systemic event will be collected on the CRF.

Table 6. Systemic Event Grading Scale: Substudy C

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

a. Only an investigator or medically qualified person is able to classify a systemic event as Grade 4.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with prespecified 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 Section 10.9.8.5.8).

8.3.5.4. Fever: Substudy C

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary for 7 days, or longer following vaccination (where Day 1 is the day of vaccination). 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 during analysis according to the scale shown in Table 7.

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), after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. 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 on the CRF.

Table 7. Scale for Fever: Substudy C

≥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)

8.3.6. Pregnancy Testing

Following screening, pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the substudy SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study if the single dose of study intervention has already been administered.

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

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

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

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

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

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including 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 provides informed consent through approximately 6 months after the participant's study vaccination, per the SoA in each substudy appendix.

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

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

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

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

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

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has 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.

8.4.1.1. Reporting SAEs to Pfizer Safety

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

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant 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, 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. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

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

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding 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 using via PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the investigator site file.

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

8.4.5.3. Occupational Exposure

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

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 will be reported to Pfizer Safety via PSSA 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

Refer to the appendix of each substudy.

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

Vaccination errors include:

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

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

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

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

Vaccination errors should be reported to Pfizer Safety within 24 hours via PSSA **only when associated with an SAE**.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

8.6.1. Specified Genetics

One or more substudies may include collection of blood samples for PBMC isolation and HLA typing; these blood samples 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-chain 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 the appendices of each substudy.

8.9. Health Economics

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

8.10. Study Procedures

See Section 10.7.8.5 for Substudy A procedures.

See Section 10.8.8.5 for Substudy B procedures.

See Section 10.9.8.5 for Substudy C procedures.

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 Hypotheses

Refer to each substudy appendix for description of statistical hypotheses.

For Substudy A, refer to Section 10.7.9.1.

For Substudy B, refer to Section 10.8.9.1.

For Substudy C, refer to Section 10.9.9.1.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Screened	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IRT system.
Safety	All participants who receive at least 1 dose of the study intervention.

For additional analysis sets, refer to the respective appendix for each substudy.

For Substudy A, refer to Section 10.7.9.2.

For Substudy B, refer to Section 10.8.9.2.

For Substudy C, refer to Section 10.9.9.2.

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 general summary of the planned statistical analyses of the endpoints.

Refer to each substudy appendix for a description of the statistical analyses for the substudy endpoints.

For Substudy A, refer to Section 10.7.9.3.

For Substudy B, refer to Section 10.8.9.3.

For Substudy C, refer to Section 10.9.9.3.

9.3.1. General Considerations

Each substudy will be reported separately.

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

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

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

9.3.1.1. Analysis for Binary Data

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

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[53] 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) and age group (< median, ≥ median). The median of baseline neutralizing titers and median age will be calculated based on the pooled data in 2 comparator groups.

9.3.1.2. Analysis for Continuous Data

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

9.3.1.2.1. Geometric Means

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

9.3.1.2.2. Geometric Mean Ratios

Model-Based GMR:

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, age, and comparison group.

Unadjusted GMR:

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

9.3.1.2.3. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points. GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.2.4. Reverse Cumulative Distribution Curves

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

9.4. Interim Analyses

Interim analyses will be determined by substudy, and details are provided in each corresponding appendix as necessary.

9.5. Sample Size Determination

9.5.1. Immunogenicity Assessment

Sample size for immunogenicity assessments will be determined by each substudy, and details are provided in each corresponding appendix.

9.5.2. Safety Assessment

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 1%, with approximately 200 participants in a vaccine group, there is 87% probability of observing at least 1 AE.

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

Assumed True Event Rate of an AE	N=50	N=100	N=200	N=300	N=400
0.1%	0.05	0.10	0.18	0.26	0.33
0.5%	0.22	0.39	0.63	0.78	0.87
1%	0.39	0.63	0.87	0.95	0.98
2%	0.64	0.87	0.98	>0.99	>0.99
3%	0.78	0.95	>0.99	>0.99	>0.99
4%	0.87	0.98	>0.99	>0.99	>0.99
5%	0.92	0.99	>0.99	>0.99	>0.99

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent/Assent Process

10.1.3.1. Informed Consent

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

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

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

The participant must be informed that 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.

The participant 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 is fully informed about their right to access and correct the participant's personal data and to withdraw consent for the processing of the participant's personal data.

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

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

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

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

10.1.3.2. Assent

The investigator or their representative will explain the nature of the study to the participant and their parent(s)/legal guardian and answer all questions regarding the study. The participant and their 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 and their parent(s)/legal guardian must be informed that their participation is voluntary. 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, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant's parent(s)/legal guardian and the study participant as applicable are 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's 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's parent(s)/legal guardian.

The participant's 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's parent(s)/legal guardian is fully informed about their right to access and correct their child's personal data and to withdraw consent for the processing of their child's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardian in certain regions.

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 the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study as required per local regulations.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

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

10.1.3.3. Electronic Consent

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

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

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

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.8. Source Documents

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

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

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

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

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

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

10.1.9. Use of Medical Records

In certain situations, sponsor review of redacted copies of participant medical records for prior COVID-19 vaccines (as applicable to the substudy), for safety reporting including AESIs, and for COVID-19 surveillance may be performed, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

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

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

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

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

10.1.10. Study and Site Start and Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;

- Inadequate recruitment of participants by the investigator;

- Discontinuation of further study intervention development.

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

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

10.1.11. Publication Policy

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

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

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

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. When applicable, editorial or technical support provided by a third party and paid for by Pfizer, or provided by a Pfizer employee, may be a reportable transfer of value under the Sunshine Act for US licensed physicians or other healthcare professionals. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.12. Sponsor's Medically Qualified Individual

Substudy A and Substudy B:

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

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

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

Substudy C:

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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

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

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

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

10.3.1. Definition of AE

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

Events <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.

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

10.3.2. Definition of an SAE

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

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

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

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

Assessment of Causality

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

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

10.3.4. Reporting of SAEs

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

SAE Reporting to Pfizer Safety via the Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the is the back-up method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either:

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

OR

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

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

OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

    - Documented bilateral oophorectomy.

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

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

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

    - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

    - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

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 and/or RNA

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

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

- The sponsor will store the DNA 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.

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

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

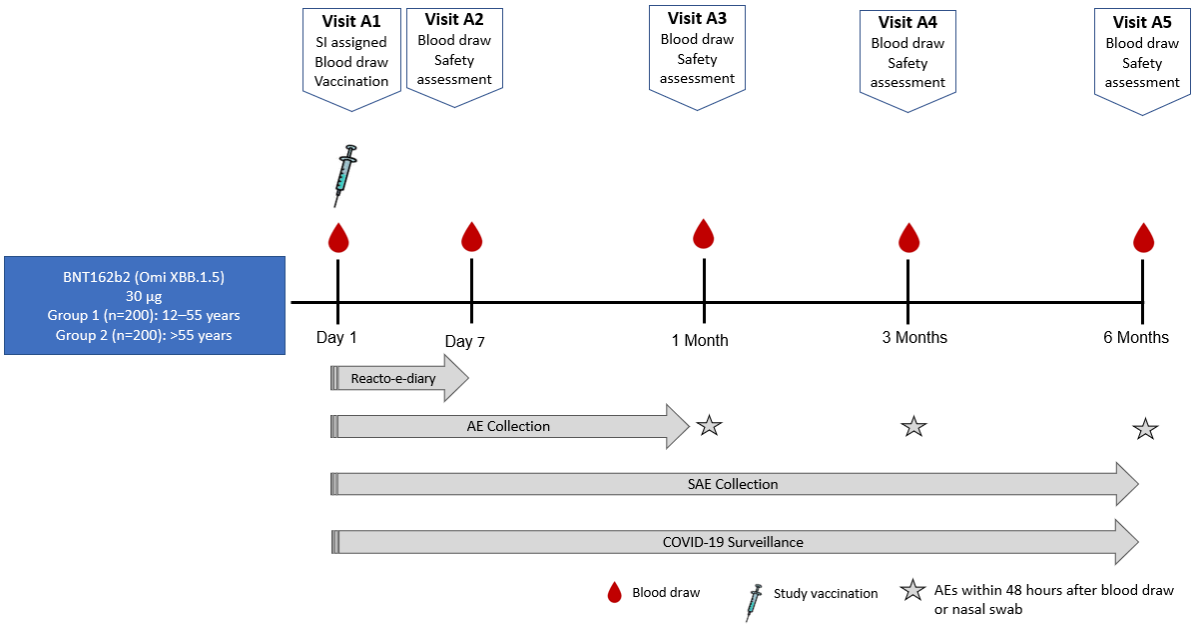
10.7. Appendix 7: Substudy A

10.7.1. Substudy A Summary

10.7.1.1. Synopsis

See Section 1.1 for the synopsis of Substudy A.

10.7.1.2. Schema



10.7.1.3. Schedule of Activities for Substudy A

Visit Identifier	A1	A2	A3	A4	A5	Unplanned	Notes
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**	**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 10.7.8.5.8**.**
Visit Window	**Day 1**	**6 to 8 Days After Visit A1**	**28 to 35 Days After Visit A1**	**84 to 98 Days After Visit A1**	**175 to 189 Days After Visit A1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**Visit A4 and Visit A5 may be performed as telehealth visits if the participant had blood draws discontinued.**
Obtain informed consent/assent	X						If vaccination is temporarily delayed, per Section 10.7.5.5, consent need not be obtained again on the day of vaccination. For participants <18 years of age (at the time of consent), the parent(s)/legal guardian will provide signed informed consent. Depending on the age of the participant and according to local requirements, participants will also be asked to provide assent as appropriate (verbal or written).
Assign participant number	X						If participant is from a prior Pfizer COVID-19 study(ies), record the participant number(s) of the prior study(ies) in the CRF.
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 8.3.6.

Visit Identifier	A1	A2	A3	A4	A5	Unplanned	Notes
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**	**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 10.7.8.5.8**.**
Visit Window	**Day 1**	**6 to 8 Days After Visit A1**	**28 to 35 Days After Visit A1**	**84 to 98 Days After Visit A1**	**175 to 189 Days After Visit A1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**Visit A4 and Visit A5 may be performed as telehealth visits if the participant had blood draws discontinued.**
Confirm use of contraceptives (if appropriate)	X	X	X				Refer to Section 5.3.1.
Measure height and weight	X						
Perform clinical assessment	X	X	X				Including, if indicated, a physical examination (Section 10.7.8.3.1).
Record nonstudy vaccine information	X	X	X	X	X	X	Refer to Section 10.7.6.9.
Record prohibited medication use		X	X	X	X	X	Refer to Section 10.7.6.9.1.
Confirm eligibility	X						Refer to Section 10.7.5.1 and Section 10.7.5.2.
Measure body temperature	X						
Review temporary delay criteria	X						See Section 10.7.5.5.
Nasal (midturbinate) swab for SARS-CoV-2 NAAT	X					X	
Blood sample for immunogenicity assessments	~50 mL/ 10 mL	~20 mL/ 10 mL	~50 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 at time of consent; 10 mL is to be collected from participants 12 through 17 years of age at time of consent. Blood sample collection may be halted or discontinued upon notification by Pfizer.

Visit Identifier	A1	A2	A3	A4	A5	Unplanned	Notes
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**	**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 10.7.8.5.8**.**
Visit Window	**Day 1**	**6 to 8 Days After Visit A1**	**28 to 35 Days After Visit A1**	**84 to 98 Days After Visit A1**	**175 to 189 Days After Visit A1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**Visit A4 and Visit A5 may be performed as telehealth visits if the participant had blood draws discontinued.**
Blood sample for PBMC isolation	~130 mL	~130 mL	~130 mL	~130 mL	~130 mL		Applicable at designated sites only. Optional with additional consent given by participants ≥18 years of age. See Section 10.7.8.2.2.
Blood sample for HLA typing	~5 mL						Applicable at designated sites only. Optional with additional consent given by participants ≥18 years of age. See Section 10.7.8.2.2.
Obtain randomization number using the IRT system	X						Refer to Section 10.7.8.5.1.
"Unblinded" staff obtains the participant's vaccine vial allocation using the IRT system	X						Refer to Section 10.7.8.5.1.
"Unblinded" staff administers 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 potential COVID-19 illness and reactogenicity e-diary completion and severe reactogenicity symptoms), assist the participant with downloading the app or issue provisioned device, if required	X						
Provide thermometer and measuring device	X						

Visit Identifier	A1	A2	A3	A4	A5	Unplanned	Notes
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**	**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 10.7.8.5.8**.**
Visit Window	**Day 1**	**6 to 8 Days After Visit A1**	**28 to 35 Days After Visit A1**	**84 to 98 Days After Visit A1**	**175 to 189 Days After Visit A1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**Visit A4 and Visit A5 may be performed as telehealth visits if the participant had blood draws discontinued.**
Provide/ensure participant has a self-swab kit in case of COVID-19 symptoms and instructions on self-collection of nasal swabs	X	X	X	X			
Ask/remind the participant to contact the site if participant experiences any severe (Grade 3) reactogenicity symptoms	X	X					
Ask/remind the participant to contact the site if a medically attended event or hospitalization occurs	X	X	X	X			
Ask/remind the participant to contact site immediately if participant experiences any symptoms as detailed in Section 10.7.8.5.7 (COVID-19 or MIS-C).	X	X	X	X			
Participant completes COVID-19 illness e-diary	←	—	—	—	→		Refer to Section 10.7.8.3.4 and Section 10.7.8.5.7.
Ask/remind the participant to contact site immediately if participant experiences any symptoms of acute chest pain, shortness of breath, or palpitations	X	X	X				Refer to Section 10.7.8.5.10.
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←	→					If Visit A2 occurs on Day 6, continue to review e-diary data through Day 7.

Visit Identifier	A1	A2	A3	A4	A5	Unplanned	Notes
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**	**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 10.7.8.5.8**.**
Visit Window	**Day 1**	**6 to 8 Days After Visit A1**	**28 to 35 Days After Visit A1**	**84 to 98 Days After Visit A1**	**175 to 189 Days After Visit A1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**Visit A4 and Visit A5 may be performed as telehealth visits if the participant had blood draws discontinued.**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X				
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	Includes nonserious AEs through Visit A3; any AEs occurring up to 48 hours after a blood draw or nasal swab collection; and SAEs or potential menstrual cycle disturbances through the end of the study (see Section 8.4.1 and Section 10.7.8.4.1).
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)						X	Refer to Section 10.7.8.2.1.
Assist the participant to delete the e-diary application or collect the provisioned device					X		

10.7.2. Introduction for Substudy A

10.7.2.1. Study Rationale

Following the guidance of the WHO, EMA, and FDA (May-June 2023) on the antigen composition of COVID-19 vaccines for the upcoming autumn/winter respiratory virus season, Pfizer/BioNTech will evaluate the safety, tolerability, and immunogenicity of the new variant-adapted vaccine, BNT162b2 (Omi XBB.1.5). Refer to Section 2.1 and Section 2.2 for further details on the rationale for this substudy.

10.7.2.2. Background

See Section 2.2 for the study background.

10.7.2.3. Benefits/Risk Assessment

No additional risks are identified for Substudy A beyond those detailed in Section 2.3.

10.7.2.4. Benefit Assessment

See Section 2.3.

10.7.3. Objectives, Estimands, and Endpoints for Substudy A

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
Safety		
To describe the safety and tolerability profile of BNT162b2 (Omi XBB.1.5) 30 µg in mRNA COVID-19 vaccine–experienced participants ≥12 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
Immunogenicity		
To describe the immune response to BNT162b2 (Omi XBB.1.5) 30 µg and to bivalent BNT162b2 (WT/Omi BA.4/BA.5)[a] 30 µg in mRNA COVID-19 vaccine–experienced participants ≥12 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT 1 month after vaccination • GMFR from before the study vaccination to 1 month after vaccination • Percentages of participants with seroresponse[b] 1 month after vaccination	• SARS-CoV-2 Omi XBB.1.5–neutralizing titers • SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers

Objectives	Estimands	Endpoints
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune response to BNT162b2 (Omi XBB.1.5) 30 µg and to bivalent BNT162b2 (WT/Omi BA.4/BA.5)[a] 30 µg in mRNA COVID-19 vaccine–experienced participants ≥12 years of age.[c]	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point • GMFR from before the study vaccination to each subsequent time point • Percentages of participants with seroresponse[b] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omi XBB.1.5–neutralizing titers • SARS-CoV-2 Omi BA.4/BA.5-neutralizing titers
To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine age group.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern)[c]		• SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the Omicron XBB.1.5 strain in a subset of participants with PBMC samples collected.		

a. The participants ≥12 years of age from Study C4591044 Cohort 2/Cohort 3 who received bivalent BNT162b2 (WT/Omi BA.4/BA.5) 30 µg will be used as a historical control for this objective.
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. Immunogenicity samples from a subset of participants may be tested for this objective.

10.7.4. Study Design for Substudy A

10.7.4.1. Overall Study Design

This is an open-label Phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of an updated vaccine against COVID-19. Participants 12 through 55 and >55 years of age who have received at least 3 prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5–adapted bivalent vaccine received at least 150 days prior to study vaccination (Visit A1/Day 1), will receive a single open-label 30-µg dose of BNT162b2 (Omi XBB.1.5). Approximately 400 participants will be enrolled. The study duration will be 6 months, with 5 scheduled visits. A reactogenicity e-diary will be used by participants for 7 days from the day of vaccination. The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 30 participants in each age group who consent to collection of optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing. See Table 9.

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

Table 9. Substudy A Design

Vaccine: BNT162b2 (Omi XBB.1.5)						
Group	**Participant Age Group**	**Prior Doses[a]**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization/ Blind**
1	12-55 Years[b]	≥3	≥150 Days	30 µg	200	Open-label
2	>55 Years	≥3	≥150 Days	30 µg	200	Open-label

a. Prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5–adapted bivalent vaccine.
b. A maximum of 50 participants aged 12 through 17 years are to be enrolled.

Participants ≥12 years of age from Study C4591044 Cohort 2/Cohort 3 who received bivalent BNT162b2 (WT/Omi BA.4/BA.5) 30 µg as a fourth dose will be used as a historical control group for immunogenicity assessment.

10.7.4.2. Scientific Rationale for Substudy A Design

See Section 10.7.2.1.

10.7.4.3. Rationale for Comparator

Study C4591044 participants ≥12 years of age who received bivalent BNT162b2 (WT/Omi BA.4/BA.5) 30 µg as a fourth dose will be used as a historical comparator, as under EUA bivalent BNT162b2 (WT/Omi BA.4/BA.5) 30 µg is the authorized vaccine to be administered to individuals in the US (under the EUA issued 31 August 2022).[6]

10.7.4.4. Justification of Dose

Refer to Section 4.5 for justification of the 30-µg dose level.

10.7.4.5. End of Study Definition

See Section 4.6.

10.7.5. Study Population for Substudy A

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.

10.7.5.1. Inclusion Criteria

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

Age and Sex:

1. Participants ≥12 years of age at Visit A1 (Day 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 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 or have parent(s)/legal guardian capable of giving signed informed consent 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 (as defined in Appendix 1, Section 10.1.3), and the participant's assent, when applicable, before any study-specific activity is performed. All 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 document.

Other Inclusion Criteria:

5. Participants who have received at least 3 prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being a US-authorized Omicron BA.4/BA.5–adapted bivalent vaccine received at least 150 days before Visit A1 (Day 1).

   Note: Documented confirmation of prior mRNA COVID-19 vaccines received must be obtained before enrollment.

10.7.5.2. Exclusion Criteria

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

Medical Conditions:

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

6. History of myocarditis or pericarditis.

Prior/Concomitant Therapy:

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

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

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

Prior/Concurrent Clinical Study Experience:

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

Other Exclusion Criteria:

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

10.7.5.3. Lifestyle Considerations

10.7.5.3.1. Contraception

See Section 5.3.1.

10.7.5.4. Screen Failures

See Section 5.4.

10.7.5.5. 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 A1 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 10.7.8.5.7).

   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 on a local test 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 at a dose of ≥20 mg/day of prednisone or equivalent. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days.

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

10.7.6. Study Interventions and Concomitant Therapy for Substudy A

10.7.6.1. Study Intervention Administered

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

- BNT162b2 (Omi XBB.1.5) =
  - (BNT162b2 Omicron XBB.1.5)
  - (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions - Substudy A	
Intervention Name	BNT162b2 (Omi XBB.1.5) BNT162b2 monovalent (Omicron XBB.1.5) Preformulated as a single vial (no dilution required)
Type	Vaccine
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	modRNA
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg
Route of Administration	Intramuscular injection
Sourcing	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in single-dose glass vials for single use as open-label supply. Vials will be labeled as required per country requirement.
SRSD	IB

Study Arms - Substudy A		
Arm Title	Group 1: 12-55 years, 30 µg	Group 2: >55 years, 30 µg
Arm Description	Participants will receive BNT162b2 (Omi XBB.1.5) 30 µg at Visit A1	Participants will receive BNT162b2 (Omi XBB.1.5) 30 µg at Visit A1

10.7.6.1.1. Administration

Participants will receive 1 dose of BNT162b2 (Omi XBB.1.5) at Visit A1 in accordance with the study's SoA. For other details regarding study intervention administration, see Section 6.1.1.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm.

10.7.6.2. Preparation, Handling, Storage, and Accountability

See Section 6.2.

10.7.6.3. Assignment to Study Intervention

See Section 6.3.

10.7.6.4. Blinding

Substudy A is an open-label study.

10.7.6.4.1. Blinding of Participants

Participants will not be blinded to their assigned study intervention. Refer to Table 9.

10.7.6.4.2. Blinding of Site Personnel

Investigators and other site staff will not be blinded to participants' assigned study intervention. However, the IRT system for this protocol is set up to accommodate multiple substudies, some of which may be observer-blind studies. Therefore, study staff assigned to the "unblinded" role, per the delegation log, will receive, store, assign, and prepare the study intervention and are considered "unblinded" study staff. The study-specific IRT reference manual and IPM provide further details.

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

10.7.6.4.3. Blinding of the Sponsor

The majority of Pfizer staff will be unblinded to participants' assigned/received study intervention. All laboratory testing personnel performing serology assays where a comparator group is also analyzed will remain blinded to the study intervention assigned/received. All laboratory personnel performing serology and PCR testing will be blinded to the participant's identity, study visit, or study cohort associated with the sample.

10.7.6.4.4. Breaking the Blind

Not applicable.

10.7.6.5. Study Intervention Compliance

See Section 6.5.

10.7.6.6. Dose Modification

See Section 6.6.

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

See Section 6.7.

10.7.6.8. Treatment of Overdose

See Section 6.8.

10.7.6.9. Prior and Concomitant Therapy

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

- Prohibited medications listed in Section 10.7.6.9.1 will be recorded in the concomitant medication CRF.
- 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.

10.7.6.9.1. 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.

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after the study vaccination, with the exception of seasonal and pandemic influenza vaccine, which 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.

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

- Receipt of short-term (<14 days) systemic corticosteroids at a dose of ≥20 mg/day of prednisone or equivalent is prohibited from 28 days prior to enrollment 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.

10.7.6.9.2. Permitted During the Study

Medication other than that described as prohibited in Section 10.7.6.9.1 required for treatment of preexisting conditions, acute illness, or to treat symptoms associated with study intervention administration is permitted.

- Inhaled, topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.
- Systemic corticosteroids administered at a dose of <20 mg/day of prednisone or equivalent are permitted.

10.7.7. Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal for Substudy A

See Section 7.1 and Section 7.2.

10.7.8. Study Assessments and Procedures for Substudy A

10.7.8.1. Administrative Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD from the participant or the participant's parent(s)/legal guardian before performing any study-specific procedures.

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.

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 wellbeing of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and

preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

10.7.8.1.1. Baseline Procedures

The baseline procedures are listed below. They are performed at Visit A1 (Day 1):

- Record demography data (including age in years, sex, race, and ethnicity). The age will be collected to critically evaluate the immune response and safety profile and to identify pediatric participants.
- 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.

10.7.8.1.2. Telehealth Visits

- Potential COVID-19 illness visits may be conducted as telehealth visits. Refer to Section 10.7.8.5.8.
- Any participants who have scheduled blood draws discontinued* may be followed for safety at Visit A4 (Month 3) and Visit A5 (Month 6) via telehealth visits. Note: Visit A1 (Day 1), Visit A2 (Week 1), and Visit A3 (Month 1) must remain as in-person visits to the site.

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

General requirements:

- Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Assessments that may be performed during a telehealth visit are described in the SoA. Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- If applicable: Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- If applicable: Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 10.4.

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

10.7.8.2. Efficacy and Immunogenicity Assessments

10.7.8.2.1. Surveillance for COVID-19 and MIS-C

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 10.7.8.5.7), for the purposes of the study he or she will be considered to potentially have COVID-19. In this circumstance, the participant 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 10.7.8.5.8) 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 to be 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;

- 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. 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, deemed necessary.

- **Confirmed severe COVID-19 (FDA definition)[54]:** 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)[55]:** confirmed COVID-19 and presence of at least 1 of the following:
  - Hospitalization;
  - Admission to the ICU;
  - Intubation or mechanical ventilation;
  - Death.

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[56]:
- 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.

10.7.8.2.2. Vaccine-Induced Immunogenicity

Blood samples will be obtained for immunogenicity testing at the central laboratory.

The SARS-CoV-2 neutralization assay will be run on serum samples obtained for the following strains:

- Omicron XBB.1.5
- Wild type
- Omicron BA.4/BA.5

At designated sites, optional whole blood samples of ~130 mL will be obtained from up to approximately 30 participants per age group for evaluation of boostability and protection against the variant strain for isolation of PBMCs. These samples will be used to describe B-cell and T-cell responses to the variant and the original strains. A blood sample of ~5 mL for HLA typing will also be obtained (at Visit A1 only). Refer to the SoA for time points of collection.

10.7.8.2.3. N-Binding Antibody Test

The N-binding antibody test will be performed by the central laboratory at certain blood sample collections to establish prior exposure to SARS-CoV-2 up to the time point. These data will be used for study analyses.

10.7.8.2.4. Biological Samples

Refer to Section 8.2.4 for general information regarding use and storage of biological samples.

The total blood sampling volume for individual participants at scheduled visits in this study is approximately 50 mL for participants 12 through 17 years of age and approximately 160 mL for participants ≥18 years of age. Those participants ≥18 years of age who consent to additional blood collection for isolation of PBMCs and additional serology will have a total blood sampling volume of up to approximately 815 mL. 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.

Blood sample collection may be halted or discontinued upon notification by Pfizer. This includes discontinuing sampling in dosed participants who are no longer eligible for the study as well as discontinuation for groups of participants or all participants.

10.7.8.3. 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.

10.7.8.3.1. 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 Sections 8.4.1 to 8.4.3.

10.7.8.3.2. Vital Signs

The participant's body temperature will be measured 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 Sections 8.4.1 to 8.4.3.

10.7.8.3.3. Clinical Safety Laboratory Assessments

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

10.7.8.3.4. Electronic Diary

E-diary assessments are included in Substudy A for participants' reporting of 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 vaccination e-diary on a daily basis, starting on the day of vaccination (Day 1) through Day 7. Refer to Section 8.3.4 for details.

The e-diary is also 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 diary on a weekly basis throughout the study and whenever they receive a diagnosis of COVID-19 or experience symptoms of COVID-19. Refer to Section 10.7.8.5.7 for details.

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

Refer to Section 8.4 and the following subsections:

- Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information
- Section 8.4.2 Methods of Detecting AEs and SAEs
- Section 8.4.3 Follow-Up of AEs and SAEs
- Section 8.4.4 Regulatory Reporting Requirements for SAEs
- Section 8.4.5 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure
- Section 8.4.6 Cardiovascular and Death Events
- Section 8.4.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs
- Section 8.4.9 Medical Device Deficiencies
- Section 8.4.10 Vaccination Errors

10.7.8.4.1. Adverse Events of Special Interest

The following events, if reported, have additional procedures associated with their evaluation; they are, therefore, considered protocol-specified AESIs:

- Confirmed diagnosis of myocarditis or pericarditis occurring within 6 weeks after vaccination. See Section 10.7.8.5.10.
- Potential menstrual cycle disturbances. See Section 10.7.8.5.11.

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

All AESIs must be reported as an AE or SAE, as appropriate, following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Report Form.

10.7.8.4.1.1. 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**.

10.7.8.4.2. Genetics

Refer to Section 8.6.

10.7.8.5. Substudy A Procedures

10.7.8.5.1. Visit A1 – Study Intervention Administration – Day 1

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian as appropriate. 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 or his/her parent(s)/legal guardian as appropriate. 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 number of both the most recent prior study and the first study in the CRF.
- Obtain the participant's demography (including age in years, sex, race, and ethnicity).
- 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 and must be mRNA COVID-19 vaccines, with the most recent dose being an Omicron BA.4/BA.5–adapted bivalent vaccine, as specified in Section 10.7.5.1, inclusion criterion 5.
- Perform a urine pregnancy test on WOCBP as described in Section 8.3.6.
- 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 10.7.8.3.1), 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 10.7.6.9.

- 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.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 10.7.5.5.

- 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 10 mL for participants 12 through 17 years of age and approximately 50 mL for participants ≥18 years of age) for testing of immunogenicity and N-binding antibody.

- If the participant is part of the group for description of cell-mediated and additional humoral immune responses (select sites only; ≥18 years of age only; additional consent required),

    - collect a blood sample (approximately 130 mL) for PBMC isolation

    - collect an additional blood sample of 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 the "unblinded" site staff role.

- Site staff member assigned to the "unblinded" role, per the delegation log, 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.

- 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 his/her parent(s)/legal guardian in downloading the study application onto the participant's own device or issue a provisioned device if required.

- Provide instructions on e-diary completion and ask the participant or his/her 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.

- Ask the participant or his/her 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.

    - Any severe systemic event.

- Ask the participant or his/her 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 his/her 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 10.7.8.5.7 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.

- 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 10.7.8.5.10).

- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her 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 a dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.7.8.5.2. Visit A2 – 1-Week Follow-Up Visit (6 to 8 Days After Visit A1)

- 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 10.7.6.9.
- Record details of any of the prohibited medications specified in Section 10.7.6.9.1 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 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 20 mL for participants ≥18 years of age) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated and additional humoral immune responses (select sites only; ≥18 years of age only; additional consent required), 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 his/her 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.
    - Any severe systemic event.
- Remind the participant or his/her 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 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 10.7.8.5.10).
- Ask the participant or his/her 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 10.7.8.5.7.
- Ensure that the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Schedule an appointment for the participant to return for the next study visit.

10.7.8.5.3. Visit A3 – 1-Month Follow-Up Visit (28-35 Days After Visit A1)

- 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 10.7.6.9.
- Record details of any of the prohibited medications specified in Section 10.7.6.9.1 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.
- Collect a blood sample (approximately 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 50 mL for participants ≥18 years of age) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only; ≥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 his/her 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 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 10.7.8.5.10).
- Ask the participant or his/her 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 10.7.8.5.7.
- Ensure that the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.7.8.5.4. Visit A4 – 3-Month Follow-Up Visit (84-98 Days After Visit A1)

- Record nonstudy vaccinations as described in Section 10.7.6.9.
- Record details of any of the prohibited medications specified in Section 10.7.6.9.1 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 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 20 mL for participants ≥18 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; ≥18 years of age only; additional consent required), collect a blood sample (approximately 130 mL) for PBMC isolation.
- Remind the participant or his/her 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 his/her 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 10.7.8.5.7.
- Ensure that the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.7.8.5.5. Visit A5 – 6-Month Follow-Up Visit (175-189 Days After Visit A1)

- Record nonstudy vaccinations as described in Section 10.7.6.9.
- Record details of any of the prohibited medications specified in Section 10.7.6.9.1 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 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 20 mL for participants ≥18 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; ≥18 years of age only; additional consent required), collect a blood sample (approximately 130 mL) for PBMC isolation.
- Collect the participant's e-diary provisioned device or assist the participant or his/her 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.

10.7.8.5.6. 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 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 his/her 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.
- The investigator or authorized designee confirmed severe reactogenicity assessment via medical records and/or telehealth assessment.

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.

10.7.8.5.7. COVID-19 and MIS-C Surveillance

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), the participant or his/her parent(s)/legal guardian is instructed to contact the site immediately. If confirmed to be a potential COVID-19 illness, the site should schedule and conduct either an in-person or telehealth visit as soon as possible, optimally within 3 days after symptom onset (and at the latest 4 days after symptom resolution). Refer to Section 10.7.8.2.1 for more details on COVID-19 and MIS-C surveillance.

- 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. 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, deemed necessary.
- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered to be 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 the vaccination, 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 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 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 as a potential COVID-19 illness; if not, the symptoms that overlap with systemic events should be recorded in the reactogenicity e-diary or as AEs, if not captured in the reactogenicity e-diary.

The participant or his/her parent(s)/legal guardian is 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.

The participant or his/her parent(s)/legal guardian may utilize a COVID-19 illness e-diary through an application (see Section 8.3.4) installed on a provisioned device or on the participant's or his/her 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, the participant or his/her parent(s)/legal guardian should be encouraged to seek care, if appropriate, from the participant's usual provider.

10.7.8.5.8. 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, videoconferencing software) remotely, thus allowing the participant 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 10.7.6.9.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 10.7.6.9.
- Record AEs as described in Section 8.4. Note: Potential COVID-19/MIS-C illnesses with their sequelae 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 or his/her parent(s)/legal guardian to self-collect a nasal (midturbinate) swab at home and ship it for assessment at the central laboratory.
- 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.
- 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, computed tomography 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.

10.7.8.5.9. SARS-CoV-2 NAAT Results

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

- Visit A1: 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.

Research laboratory–generated positive results from the vaccination visit swabs, and all results from the illness visit swabs, will be provided to the site at the end of the study and, therefore, cannot be relied upon to direct clinical care. The participant or his/her parent(s)/legal guardian should be directed to seek additional testing through the participant's primary healthcare provider at a licensed clinical laboratory when the participant is exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing, as per local guidance.

10.7.8.5.10. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports the following within 6 weeks after the study vaccination:

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

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 and Section 8.4.3). Other diagnoses should be recorded as AEs or SAEs, as appropriate. Refer also to Section 10.7.8.4.1.

10.7.8.5.11. Additional Procedures for Monitoring of Potential Menstrual Cycle Disturbances

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

10.7.8.5.12. Communication and Use of Technology

In a study of this nature that requires events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant 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, 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 to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary) – see Section 10.7.8.5.7.
- If a participant or his/her parent(s)/legal guardian 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 to ascertain why and also to obtain details of any missed events.
- Messages of thanks and encouragement from the study team.

10.7.9. Statistical Considerations for Substudy A

See Section 9 for general protocol statistical considerations and see specific Substudy A statistical considerations below.

10.7.9.1. Statistical Hypotheses

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

10.7.9.1.1. Estimands

The estimands corresponding to the primary objectives are described in the table in Section 10.7.3.

The safety primary objective evaluations are based on the safety population. In general, completely missing reactogenicity data (ie, all 7 days of collection were missing) will not be imputed. For partially 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 10.7.9.2). 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.

10.7.9.1.2. Multiplicity Adjustment

No multiplicity adjustment is needed for the study, as there is no statistical hypothesis.

10.7.9.2. Analysis Sets

For the purpose of analysis, in addition to the analysis sets defined in Section 9.2, the following analysis sets are defined for this substudy:

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

10.7.9.3. 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 substudy endpoints.

10.7.9.3.1. General Considerations

Refer to Section 9.3.1 for general considerations of statistical analyses.

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

Endpoint	Statistical Analysis Methods
Safety	Descriptive statistics will be provided for each reactogenicity endpoint by age subgroup (12-17 years, 18-55 years, >55 years) and overall. Local reactions and systemic events from Day 1 through Day 7 after each vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs from the study vaccination through 1 month and SAEs from the study vaccination through 6 months after the study vaccination will be provided by age subgroup and overall.
Immunogenicity	For each vaccine group, the BNT162b2 (Omi XBB.1.5) group in this substudy and the historical control of bivalent BNT162b2 (WT/Omi BA.4/BA.5) group, • GMTs and 2-sided 95% CIs of SARS-CoV-2 Omi XBB.1.5–neutralizing titers and SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers at 1 month after study vaccination will be provided for each age subgroup, overall and by baseline SARS-CoV-2 infection status. Statistical methods are described in Section 9.3.1.2.1. • GMFRs of SARS-CoV-2 XBB.1.5–neutralizing titers and SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers from baseline (before the study vaccination) to 1 month after study vaccination, along with the associated 2-sided 95% CIs, will be provided for each age subgroup, overall and by baseline SARS-CoV-2 infection status. Statistical methods are described in Section 9.3.1.2.3. • The percentages of participants with seroresponse to SARS-CoV-2 Omi XBB.1.5 and SARS-CoV-2 Omi BA.4/BA.5 at 1 month after vaccination and the associated Clopper-Pearson 95% CIs will be provided for each age subgroup, overall and by baseline SARS-CoV-2 infection status.

10.7.9.3.3. Exploratory Endpoints Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	GMTs, GMFRs, and percentages of participants with seroresponse to SARS-CoV-2 Omi XBB.1.5 and SARS-CoV-2 Omi BA.4/BA.5 at each time point, along with the associated 95% CIs, will be summarized in the same way as for the immunogenicity primary endpoints described above. This analysis may be conducted in a selected subset of participants.
COVID-19 cases	Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized.
Immune response to emerging variants	For emerging variants (under monitoring, of interest, and/or of concern) not already specified, GMTs, GMFRs, and percentages of participants with seroresponse at the specific time point, along with the associated 95% CIs, will be summarized in the same way as for the immunogenicity primary endpoints described above. This analysis may be conducted in a selected subset of participants.
Cell-mediated immune response	The cell-mediated immune response and additional humoral immune response parameters to the Omicron XBB.1.5 strain will be summarized at each time point for the subset of participants with PBMC samples collected in each group.

10.7.9.4. Interim Analyses

No formal interim analysis will be conducted. As this is a sponsor–open-label study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in Section 10.7.9.4.1.

10.7.9.4.1. Analysis Timing

At a minimum, statistical analyses will be carried out when the following data are available:

- Safety and immunogenicity data through Visit A3 (1 month after study vaccination).
- Safety and immunogenicity data through Visit A5 (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.

10.7.9.5. Sample Size Determination

The sample size is not based on any formal hypothesis test. All statistical analyses will be descriptive.

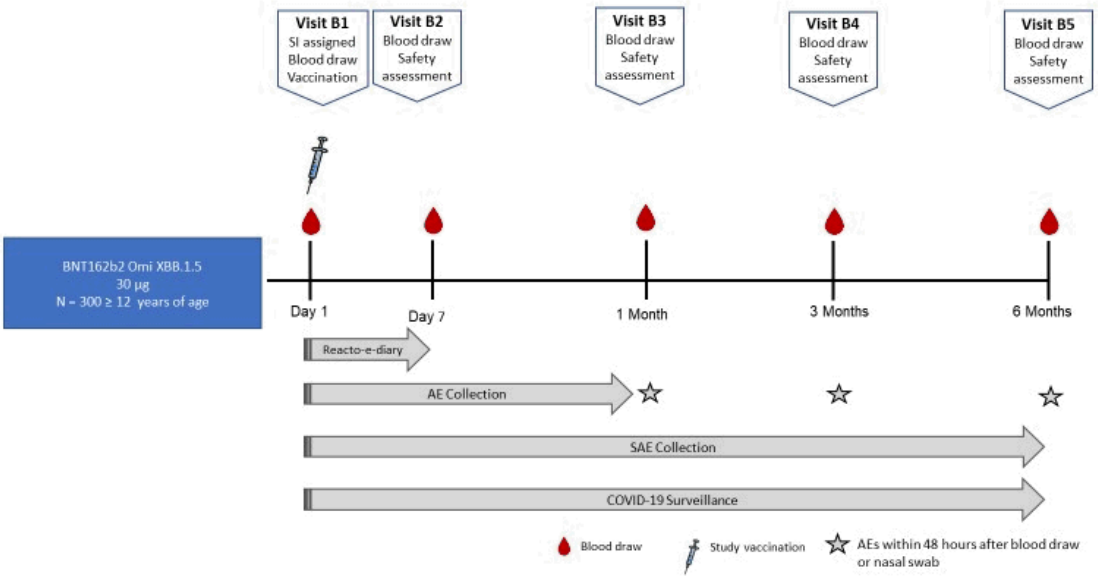
10.8. Appendix 8: Substudy B

10.8.1. Substudy B Summary

10.8.1.1. Synopsis

See Section 1.1 for the synopsis of Substudy B.

10.8.1.2. Schema



10.8.1.3. Schedule of Activities for Substudy B

Visit Identifier	B1	B2	B3	B4	B5	Unplanned	Notes
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**	**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 10.8.8.5.8**.**
Visit Window	**Day 1**	**6 to 8 Days After Visit B1**	**28 to 35 Days After Visit B1**	**84 to 98 Days After Visit B1**	**175 to 189 Days After Visit B1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**Visit B4 and Visit B5 may be performed as telehealth visits if the participant had blood draws discontinued.**
Obtain informed consent/assent	X						If vaccination is temporarily delayed, per Section 10.8.5.5, consent need not be obtained again on the day of vaccination. For participants <18 years of age (at the time of consent), the parent(s)/legal guardian will provide signed informed consent. Depending on the age of the participant and according to local requirements, participants will also be asked to provide assent as appropriate (verbal or written).
Assign participant number	X						
Obtain demography and medical history data (including positive SARS-CoV-2 test result)	X						
Urine pregnancy test (if appropriate)	X						Refer to Section 8.3.6.
Confirm use of contraceptives (if appropriate)	X	X	X				Refer to Section 5.3.1.
Measure height and weight	X						
Perform clinical assessment	X	X	X				Including, if indicated, a physical examination (Section 10.8.8.3.1).

Visit Identifier	B1	B2	B3	B4	B5	Unplanned	Notes
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**	**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 10.8.8.5.8**.**
Visit Window	**Day 1**	**6 to 8 Days After Visit B1**	**28 to 35 Days After Visit B1**	**84 to 98 Days After Visit B1**	**175 to 189 Days After Visit B1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**Visit B4 and Visit B5 may be performed as telehealth visits if the participant had blood draws discontinued.**
Record nonstudy vaccine information	X	X	X	X	X	X	Refer to Section 10.8.6.9.
Record prohibited medication use		X	X	X	X	X	Refer to Section 10.8.6.9.1.
Confirm eligibility	X						Refer to Section 10.8.5.1 and Section 10.8.5.2.
Measure body temperature	X						
Review temporary delay criteria	X						See Section 10.8.5.5.
Nasal (midturbinate) swab for SARS-CoV-2 NAAT	X					X	
Blood sample for immunogenicity assessments	~50 mL/ 10 mL	~20 mL/ 10 mL	~50 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 at time of consent; 10 mL is to be collected from participants 12 through 17 years of age at time of consent. 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. Optional with additional consent given by participants ≥18 years of age. See Section 10.8.8.2.2.

Visit Identifier	B1	B2	B3	B4	B5	Unplanned	Notes
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**	**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 10.8.8.5.8**.**
Visit Window	**Day 1**	**6 to 8 Days After Visit B1**	**28 to 35 Days After Visit B1**	**84 to 98 Days After Visit B1**	**175 to 189 Days After Visit B1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**Visit B4 and Visit B5 may be performed as telehealth visits if the participant had blood draws discontinued.**
Blood sample for HLA typing	~5 mL						Applicable at designated sites only. Optional with additional consent given by participants ≥18 years of age. See Section 10.8.8.2.2.
Obtain randomization number using the IRT system	X						Refer to Section 10.8.6.4.2.
"Unblinded" staff obtains the participant's vaccine vial allocation using the IRT system	X						Refer to Section 10.8.6.4.2.
"Unblinded" staff administers 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 potential COVID-19 illness and reactogenicity e-diary completion and severe reactogenicity symptoms), assist the participant with downloading the app or issue provisioned device, if required	X						
Provide thermometer and measuring device	X						
Provide/ensure participant has a self-swab kit in case of COVID-19 symptoms and instructions on self-collection of nasal swabs	X	X	X	X			

Visit Identifier	B1	B2	B3	B4	B5	Unplanned	Notes
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**	**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 10.8.8.5.8**.**
Visit Window	**Day 1**	**6 to 8 Days After Visit B1**	**28 to 35 Days After Visit B1**	**84 to 98 Days After Visit B1**	**175 to 189 Days After Visit B1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**Visit B4 and Visit B5 may be performed as telehealth visits if the participant had blood draws discontinued.**
Ask/remind the participant to contact the site if participant experiences any severe (Grade 3) reactogenicity symptoms	X	X					
Ask/remind the participant to contact the site if a medically attended event or hospitalization occurs	X	X	X	X			
Ask/remind the participant to contact site immediately if participant experiences any symptoms as detailed in Section 10.8.8.5.7 (COVID-19 or MIS-C).	X	X	X	X			
Participant completes COVID-19 illness e-diary	←	—	—	—	→		Refer to Section 10.8.8.3.4 and Section 10.8.8.5.7.
Ask/remind the participant to contact site immediately if participant experiences any symptoms of acute chest pain, shortness of breath, or palpitations	X	X	X				Refer to Section 10.8.8.5.10.
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←	→					If Visit B2 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				

Visit Identifier	B1	B2	B3	B4	B5	Unplanned	Notes
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**	**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 10.8.8.5.8**.**
Visit Window	**Day 1**	**6 to 8 Days After Visit B1**	**28 to 35 Days After Visit B1**	**84 to 98 Days After Visit B1**	**175 to 189 Days After Visit B1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**Visit B4 and Visit B5 may be performed as telehealth visits if the participant had blood draws discontinued.**
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	Includes nonserious AEs through Visit B3; any AEs occurring up to 48 hours after a blood draw or nasal swab collection; and SAEs or potential menstrual cycle disturbances through the end of the study (see Section 8.4.1 and Section 10.8.8.4.1).
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)						X	Refer to Section 10.8.8.2.1.
Assist the participant to delete the e-diary application or collect the provisioned device					X		

10.8.2. Introduction for Substudy B

10.8.2.1. Study Rationale

On 18 April 2023, the FDA amended the BNT162b2 EUA to simplify the vaccination schedule for most individuals, including that most unvaccinated individuals may receive a single dose of a variant-modified vaccine (rather than 2 doses). The effectiveness of a single dose was supported by observational data from England on the effectiveness of 1 dose of monovalent BNT162b2, and that, among individuals 12 to 17 years of age who had received only 1 dose of BNT162b2, those who had evidence of previous infection with Alpha, Delta, or Omicron variants had increased protection against symptomatic Omicron infection compared with those who had no evidence of previous infection.[8]

To supplement real-world evidence that a single dose is effective, results from this substudy will fill the evidence gap for use of the single dose of BNT162b2 in individuals 12 years of age and older who have not been previously vaccinated with a COVID-19 vaccine.

10.8.2.2. Background

See Section 2.2 for the study background.

10.8.2.3. Benefits/Risk Assessment

No additional risks are identified for Substudy B beyond those detailed in Section 2.3.

10.8.2.4. Benefit Assessment

See Section 2.3.

10.8.3. Objectives, Estimands, and Endpoints for Substudy B

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
Safety		
To describe the safety and tolerability profile of BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants, who were previously SARS-CoV-2 exposed, ≥12 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

Objectives	Estimands	Endpoints
Immunogenicity		
To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse[a] rate of the anti-XBB.1.5 immune response elicited by BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants, who were previously SARS-CoV-2 exposed, ≥12 years of age compared to BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the SARS-CoV-2 XBB.1.5–neutralizing titers 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants to 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A. • The difference in percentages of participants with seroresponse[a] to the XBB.1.5 strain at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participant compared to 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A.	• SARS-CoV-2 Omi XBB.1.5–neutralizing titers
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune response to BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants, who were previously SARS-CoV-2 exposed, ≥12 years of age, and BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A.[b]	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point • GMFR from before the study vaccination to each subsequent time point • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omi XBB.1.5–neutralizing titers
To describe confirmed COVID-19 and severe COVID-19 cases.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern).[b]		• SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified

Objectives	Estimands	Endpoints
To describe the cell-mediated immune response, and additional humoral immune response parameters to the Omicron XBB.1.5 strain in a subset of participants with PBMC samples collected.		

a. 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.
b. Immunogenicity samples from a subset of participants may be tested for this objective.

10.8.4. Study Design for Substudy B

10.8.4.1. Overall Study Design

This is an open-label Phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of an updated vaccine against COVID-19. Participants ≥12 years of age who were previously exposed to SARS-CoV-2 and are COVID-19 vaccine naïve will receive a single 30-µg dose of BNT162b2 (Omi XBB.1.5). Approximately 300 participants will be enrolled. The study duration will be 6 months, with 5 scheduled visits. A reactogenicity e-diary will be used by participants for 7 days from the day of vaccination. The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 30 participants aged ≥18 years who consent to collection of optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing. See Table 10.

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

Table 10. Substudy B Design

Vaccine: BNT162b2 (Omi XBB.1.5)						
Group	**Participant Age Group**	**Prior Doses**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization/ Blind**
1	≥12 Years	0		30 µg	300	Open-label

Participants from C4591054 Substudy A who received BNT162b2 (Omi XBB.1.5) 30 µg will be used as a control group to assess the immunogenicity objectives.

10.8.4.2. Scientific Rationale for Substudy B Design

See Section 10.8.2.1.

10.8.4.3. Rationale for Comparator

Study C4591054 Substudy A will be used as a contemporaneous comparator as it consists of COVID-19 vaccine–experienced participants who have BNT162b2 (Omi XBB.1.5) administered with immunogenicity sampling at the same time points (before vaccination, 1 week after dose administration, and 1, 3, and 6 months after dose administration).

10.8.4.4. Justification of Dose

Refer to Section 4.5 for justification of the 30-µg dose level.

10.8.4.5. End of Study Definition

See Section 4.6.

10.8.5. Study Population for Substudy B

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.

10.8.5.1. Inclusion Criteria

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

Age and Sex:

1. Participants ≥12 years of age at Visit B1 (Day 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 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, have parent(s)/legal guardian capable of giving signed informed consent 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 (and assent) from each study participant (as defined in Appendix 1, Section 10.1.3), and the participant's assent, when applicable, before any study-specific activity is performed. All 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 document.

Other Inclusion Criteria:

5. Participants who are COVID-19 vaccinenaïve.

6. Participants who have had any positive SARS-CoV-2 test result >28 days before study intervention administration.

10.8.5.2. Exclusion Criteria

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

6. History of myocarditis or pericarditis.

Prior/Concomitant Therapy:

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

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

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

Prior/Concurrent Clinical Study Experience:

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

Other Exclusion Criteria:

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

10.8.5.3. Lifestyle Considerations

10.8.5.3.1. Contraception

See Section 5.3.1.

10.8.5.4. Screen Failures

See Section 5.4.

10.8.5.5. 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 B1 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 10.8.8.5.7).

   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 local test positive result 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 at a dose of ≥20 mg/day of prednisone or equivalent. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days.

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

10.8.6. Study Interventions and Concomitant Therapy for Substudy B

10.8.6.1. Study Intervention Administered

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

- BNT162b2 (Omi XBB.1.5) =
  - (BNT162b2 Omicron XBB.1.5)
  - (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions - Substudy B	
Intervention Name	BNT162b2 (Omi XBB.1.5) BNT162b2 monovalent (Omicron XBB.1.5) Preformulated as a single vial (no dilution required)
Type	Vaccine
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	modRNA
Unit Dose Strength(s)	100 µg/mL

Study Interventions - Substudy B	
Dosage Level(s)	30 µg
Route of Administration	Intramuscular injection
Sourcing	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in single-dose glass vials for single use as open-label supply. Vials will be labeled as required per country requirement.
SRSD	IB

10.8.6.1.1. Administration

Participants will receive 1 dose of BNT162b2 (Omi XBB.1.5) at Visit B1 in accordance with the study's SoA. For other details regarding study intervention administration, see Section 6.1.1.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm.

10.8.6.2. Preparation, Handling, Storage, and Accountability

See Section 6.2.

10.8.6.3. Assignment to Study Intervention

See Section 6.3.

10.8.6.4. Blinding

Substudy B is an open-label study.

10.8.6.4.1. Blinding of Participants

Participants will not be blinded to their assigned study intervention. Refer to Table 10.

10.8.6.4.2. Blinding of Site Personnel

Investigators and other site staff will not be blinded to participants' assigned study intervention. However, the IRT system for this protocol is set up to accommodate multiple substudies, some of which may be observer-blind studies. Therefore, study staff assigned to the "unblinded" role, per the delegation log, will receive, store, assign, and prepare the study intervention and are considered "unblinded" study staff. The study-specific IRT reference manual and IPM provide further details.

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

10.8.6.4.3. Blinding of the Sponsor

The majority of Pfizer staff will be unblinded to participants' assigned/received study intervention. All laboratory testing personnel performing serology assays where a comparator group is also analyzed will remain blinded to the study intervention assigned/received. All laboratory personnel performing serology and PCR testing will be blinded to the participant's identity, study visit, or study cohort associated with the sample.

10.8.6.4.4. Breaking the Blind

Not applicable.

10.8.6.5. Study Intervention Compliance

See Section 6.5.

10.8.6.6. Dose Modification

See Section 6.6.

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

See Section 6.7.

10.8.6.8. Treatment of Overdose

See Section 6.8.

10.8.6.9. Prior and Concomitant Therapy

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

- Prohibited medications listed in Section 10.8.6.9.1 will be recorded in the concomitant medication CRF.
- 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.
- 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.

10.8.6.9.1. 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.

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after the study vaccination, with the exception of seasonal and pandemic influenza vaccine, which 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.

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

- Receipt of short-term (<14 days) systemic corticosteroids at a dose of ≥20 mg/day of prednisone or equivalent is prohibited from 28 days prior to enrollment 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.

10.8.6.9.2. Permitted During the Study

- Medication other than that described as prohibited in Section 10.8.6.9.1 required for treatment of preexisting conditions, acute illness, or to treat symptoms associated with study intervention administration is permitted.

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

- Systemic corticosteroids administered at a dose of <20 mg/day of prednisone or equivalent are permitted.

10.8.7. Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal for Substudy B

See Section 7.1 and Section 7.2.

10.8.8. Study Assessments and Procedures for Substudy B

10.8.8.1. Administrative Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD from the participant or the participant's parent(s)/legal guardian before performing any study-specific procedures.

A participant number will be assigned.

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.

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

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

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

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

10.8.8.1.1. Baseline Procedures

The baseline procedures are listed below. They are performed at Visit B1 (Day 1):

- Record demography data (including age in years, sex, race, and ethnicity). Age will be collected to critically evaluate the immune response and safety profile and to identify pediatric participants.
- Record any medical history of clinical significance, including positive SARS-CoV-2 test result.
- Measure and record height and weight.

10.8.8.1.2. Telehealth Visits

- Potential COVID-19 illness visits may be conducted as telehealth visits. Refer to Section 10.8.8.5.8.

- Any participants who have scheduled blood draws discontinued* may be followed for safety at Visit B4 (Month 3) and Visit B5 (Month 6) via telehealth visits. Note: Visit B1 (Day 1), Visit B2 (Week 1), and Visit B3 (Month 1) must remain as in-person visits to the site.

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

General requirements:

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

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

10.8.8.2. Efficacy and Immunogenicity Assessments

10.8.8.2.1. Surveillance for COVID-19 and MIS-C

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 10.8.8.5.7), for the purposes of the study he or she will be considered to potentially have COVID-19. In this circumstance, the participant 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 10.8.8.5.8) 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 to be 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;
  - 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. 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, deemed necessary.
- **Confirmed severe COVID-19 (FDA definition):**[54] 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)**:[55] confirmed COVID-19 and presence of at least 1 of the following:
  - Hospitalization;
  - Admission to the ICU;
  - Intubation or mechanical ventilation;
  - Death.

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:[56]

- 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.

10.8.8.2.2. Vaccine-Induced Immunogenicity

Blood samples will be obtained for immunogenicity testing at the central laboratory.

The SARS-CoV-2 neutralization assay will be run on serum samples obtained for the following strain:

- Omicron XBB.1.5

At designated sites, optional whole blood samples of ~130 mL will be obtained from up to approximately 30 participants (≥18 years of age only) for evaluation of boostability and protection against the variant strain for isolation of PBMCs. These samples will be used to describe B-cell and T-cell responses to the variant and the original strains. A blood sample of ~5 mL for HLA typing will also be obtained (at Visit B1 only). Refer to the SoA for time points of collection.

10.8.8.2.3. N-Binding Antibody Test

The N-binding antibody test will be performed by the central laboratory at certain blood sample collections to establish prior exposure to SARS-CoV-2 up to the time point. These data will be used for study analyses.

10.8.8.2.4. Biological Samples

Refer to Section 8.2.4 for general information regarding use and storage of biological samples.

The total blood sampling volume for individual participants at scheduled visits in this study is approximately 50 mL for participants 12 through 17 years of age and approximately 160 mL for participants ≥18 years of age. Those participants ≥18 years of age who consent to additional blood collection for isolation of PBMCs and additional serology will have a total blood sampling volume of up to approximately 815 mL. 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.

Blood sample collection may be halted or discontinued upon notification by Pfizer. This includes discontinuing sampling in dosed participants who are no longer eligible for the study as well as discontinuation for groups of participants or all participants.

10.8.8.3. 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.

10.8.8.3.1. 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 Sections 8.4.1 to 8.4.3.

10.8.8.3.2. Vital Signs

The participant's body temperature will be measured 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 Sections 8.4.1 to 8.4.3.

10.8.8.3.3. Clinical Safety Laboratory Assessments

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

10.8.8.3.4. Electronic Diary

E-diary assessments are included in Substudy B for participants' reporting of 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 vaccination e-diary on a daily basis, starting on the day of vaccination (Day 1) through Day 7. Refer to Section 8.3.4 for details.

The e-diary is also 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. Refer to Section 10.8.8.5.7 for details.

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

Refer to Section 8.4 and the following subsections:

- Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information
- Section 8.4.2 Methods of Detecting AEs and SAEs
- Section 8.4.3 Follow-Up of AEs and SAEs
- Section 8.4.4 Regulatory Reporting Requirements for SAEs
- Section 8.4.5 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure
- Section 8.4.6 Cardiovascular and Death Events
- Section 8.4.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs
- Section 8.4.9 Medical Device Deficiencies
- Section 8.4.10 Vaccination Errors

10.8.8.4.1. Adverse Events of Special Interest

The following events, if reported, have additional procedures associated with their evaluation; they are, therefore, considered protocol-specified AESIs:

- Confirmed diagnosis of myocarditis or pericarditis occurring within 6 weeks after vaccination. See Section 10.8.8.5.10.
- Potential menstrual cycle disturbances. See Section 10.8.8.5.11.

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

All AESIs must be reported as an AE or SAE, as appropriate, following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Report Form.

10.8.8.4.1.1. 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**.

10.8.8.4.2. Genetics

Refer to Section 8.6.

10.8.8.5. Substudy B Procedures

10.8.8.5.1. Visit B1 – Study Intervention Administration – Day 1

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian as appropriate. 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 or his/her parent(s)/legal guardian as appropriate. 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.
- Obtain the participant's demography (including age in years, sex, race, and ethnicity).
- 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.
- Perform a urine pregnancy test on WOCBP as described in Section 8.3.6.
- 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 10.8.8.3.1), 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 10.8.6.9.
- 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.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 10.8.5.5.
- 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 10 mL for participants 12 through 17 years of age and approximately 50 mL for participants ≥18 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 responses (select sites only; ≥18 years of age only; additional consent required),
    - collect a blood sample (approximately 130 mL) for PBMC isolation.
    - collect a 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 the "unblinded" site staff role.
- Site staff member assigned to the "unblinded" role per the delegation log 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.
- 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 his/her parent(s)/legal guardian in downloading the study application onto the participant's own device or issue a provisioned device if required.

- Provide instructions on e-diary completion and ask the participant or his/her 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.

- Ask the participant or his/her 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.

    - Any severe systemic event.

- Ask the participant or his/her 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 his/her 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 10.8.8.5.7 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.

- 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 10.8.8.5.10).

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

- Remind the participant or his/her 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 a dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.8.8.5.2. Visit B2 – 1-Week Follow-Up Visit (6 to 8 Days After Visit B1)

- 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 10.8.6.9.
- Record details of any of the prohibited medications specified in Section 10.8.6.9.1 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 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 20 mL for participants ≥18 years of age) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune responses (select sites only; ≥18 years of age only; additional consent required), 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 his/her 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.
- Any severe systemic event.

- Remind the participant or his/her 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 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 10.8.8.5.10).
- Ask the participant or his/her 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 10.8.8.5.7.
- Ensure that the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Schedule an appointment for the participant to return for the next study visit.

10.8.8.5.3. Visit B3 – 1-Month Follow-Up Visit (28-35 Days After Visit B1)

- 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 10.8.6.9.
- Record details of any of the prohibited medications specified in Section 10.8.6.9.1 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.
- Collect a blood sample (approximately 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 50 mL for participants ≥18 years of age) for immunogenicity testing.

- If the participant is part of the group for description of cell-mediated immune response (select sites only; ≥18 years of age only; additional consent required), 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 his/her 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 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 10.8.8.5.10).

- Ask the participant or his/her 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 10.8.8.5.7.

- Ensure that the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.

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

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

10.8.8.5.4. Visit B4 – 3-Month Follow-Up Visit (84-98 Days After Visit B1)

- Record nonstudy vaccinations as described in Section 10.8.6.9.

- Record details of any of the prohibited medications specified in Section 10.8.6.9.1 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 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 20 mL for participants ≥18 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; ≥18 years of age only; additional consent required), collect a blood sample (approximately 130 mL) for PBMC isolation.

- Remind the participant or his/her 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 his/her 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 10.8.8.5.7.
- Ensure that the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.8.8.5.5. Visit B5 – 6-Month Follow-Up Visit (175-189 Days After Visit B1)

- Record nonstudy vaccinations as described in Section 10.8.6.9.
- Record details of any of the prohibited medications specified in Section 10.8.6.9.1 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 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 50 mL for participants ≥18 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; ≥18 years of age only; additional consent required), collect a blood sample (approximately 130 mL) for PBMC isolation.
- Collect the participant's e-diary provisioned device or assist the participant or his/her 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.

10.8.8.5.6. 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 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 his/her 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.
- The investigator or authorized designee confirmed severe reactogenicity assessment via medical records and/or telehealth assessment.

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.

10.8.8.5.7. COVID-19 and MIS-C Surveillance

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), the participant or his/her parent(s)/legal guardian is instructed to contact the site immediately. If confirmed to be a potential COVID-19 illness, the site should schedule and conduct either an in-person or telehealth visit as soon as possible, optimally within 3 days after symptom onset (and at the latest 4 days after symptom resolution). Refer to Section 10.8.8.2.1 for more details on COVID-19 and MIS-C surveillance.

- 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. 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, deemed necessary.
- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered to be 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 the vaccination, 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 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 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 as a potential COVID-19 illness; if not, the symptoms that overlap with systemic events should be recorded in the reactogenicity e-diary or as AEs, if not captured in the reactogenicity e-diary.

The participant or his/her parent(s)/legal guardian is 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.

The participant or his/her parent(s)/legal guardian may utilize a COVID-19 illness e-diary through an application (see Section 8.3.4) installed on a provisioned device or on the participant's or his/her 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, the participant or his/her parent(s)/legal guardian should be encouraged to seek care, if appropriate, from the participant's usual provider.

10.8.8.5.8. 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, videoconferencing software) remotely, thus allowing the participant 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 10.8.6.9.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 10.8.6.9.
- Record AEs as described in Section 8.4. Note: Potential COVID-19/MIS-C illnesses with their sequelae 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 or his/her parent(s)/legal guardian to self-collect a nasal (midturbinate) swab at home and ship it for assessment at the central laboratory.
- 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.
- 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, computed tomography 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.

10.8.8.5.9. SARS-CoV-2 NAAT Results

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

- Visit B1: 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.

Research laboratory–generated positive results from the vaccination visit swabs, and all results from the illness visit swabs, will be provided to the site at the end of the study and, therefore, cannot be relied upon to direct clinical care. The participant or his/her parent(s)/legal guardian should be directed to seek additional testing through the participant's primary healthcare provider at a licensed clinical laboratory when the participant is exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing, as per local guidance.

10.8.8.5.10. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports the following within 6 weeks after the study vaccination:

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

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 and Section 8.4.3). Other diagnoses should be recorded as AEs or SAEs, as appropriate. Refer also to Section 10.8.8.4.1.

10.8.8.5.11. Additional Procedures for Monitoring of Potential Menstrual Cycle Disturbances

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

10.8.8.5.12. Communication and Use of Technology

In a study of this nature that requires events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant 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, as appropriate, and the study site staff will be established. The participant or the participant's 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 to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary) – see Section 10.8.8.5.7.
- If a participant or his/her parent(s)/legal guardian 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 to ascertain why and also to obtain details of any missed events.
- Messages of thanks and encouragement from the study team.

10.8.9. Statistical Considerations for Substudy B

See Section 9 for general protocol statistical considerations and see specific Substudy B statistical considerations below.

10.8.9.1. Statistical Hypotheses

The immunogenicity primary objective is to assess the noninferiority with respect to level of neutralizing titer and seroresponse rate of the anti-XBB.1.5 immune response induced by BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants who were previously exposed to SARS-CoV-2 relative to the immune response elicited by BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A. 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 Omi XBB.1.5–neutralizing titers measured at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants who were previously exposed to SARS-CoV-2;

  - $\text{Ln}(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omi XBB.1.5–neutralizing titers measured at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A.

- 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 Omi XBB.1.5 strain at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants who were previously exposed to SARS-CoV-2;

  - p_2 is the percentage of participants with seroresponse to the Omi XBB.1.5 strain at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A.

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

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 greater than -10%.

10.8.9.1.1. Estimands

The estimands corresponding to the primary objectives are described in the table in Section 10.8.3.

The safety primary objective evaluations are based on the safety population. In general, completely missing reactogenicity data (ie, all 7 days of collection were missing) will not be imputed. For partially 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 10.8.9.2). 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.

10.8.9.1.2. Multiplicity Adjustment

The 2 hypotheses for the primary objective will be evaluated sequentially using a 1-sided alpha of 0.025. Noninferiority based on GMR will be evaluated first, followed by seroresponse rate difference.

10.8.9.2. Analysis Sets

For the purpose of analysis, in addition to the analysis sets defined in Section 9.2, the following analysis sets are defined for this substudy:

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

10.8.9.3. 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 substudy endpoints.

10.8.9.3.1. General Considerations

Refer to Section 9.3.1 for general considerations of statistical analyses.

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

Endpoint	Statistical Analysis Methods
Safety	Descriptive statistics will be provided for each reactogenicity endpoint by age subgroup (12-17 years, 18-55 years, >55 years) and overall. Local reactions and systemic events from Day 1 through Day 7 after each vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs from the study vaccination through 1 month and SAEs from the study vaccination through 6 months after the study vaccination will be provided by age subgroup and overall.
Immunogenicity	• GMR of SARS-CoV-2 Omi XBB.1.5–neutralizing titers at 1 month after the study vaccination and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.2. As the primary approach to calculate the GMR and CI for neutralizing titer, a linear regression model that includes terms for baseline neutralizing titer, age, 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 SARS-CoV-2 Omi XBB.1.5 strain at 1 month after the study vaccination will be provided for each group. 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). The primary approach to calculate the difference in seroresponse rate between 2 comparison groups and the associated 95% CI will be the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median) and age group (< median, ≥ median). • 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%.

10.8.9.3.3. Exploratory Endpoints Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	• For COVID-19 vaccine–naïve participants in this substudy and control group of vaccine-experienced participants from Substudy A, • GMTs and 2-sided 95% CIs of SARS-CoV-2 Omi XBB.1.5–neutralizing titers at each time point will be provided for each group, by age subgroup and overall. The statistical methods are described in Section 9.3.1.2.1. • GMFRs of SARS-CoV-2 Omi XBB.1.5–neutralizing titers from baseline (before the study vaccination) to each time point after study vaccination, along with the associated 2-sided 95% CIs, will be provided for each group, by age subgroup and overall. Statistical methods are described in Section 9.3.1.2.3. • The percentages of participants with seroresponse to SARS-CoV-2 Omicron XBB.1.5 at each time point after vaccination and the associated Clopper-Pearson 95% CIs will be provided for each group, by age subgroup and overall. This analysis may be conducted in a selected subset of participants. For control group participants from Substudy A, the above analysis may be performed by baseline SARS-CoV-2 infection status if there is a sufficient number of participants without prior SARS-CoV-2 infection.
COVID-19 cases	• Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized.
Immune response to emerging variants	For emerging variants (under monitoring, of interest, and/or of concern) not already specified, GMTs, GMFRs, and percentages of participants with seroresponse at the specific time point, along with the associated 95% CIs, will be summarized in the same way as for the exploratory immunogenicity endpoints described above. This analysis may be conducted in a selected subset of participants.
Cell-mediated immune response	The cell-mediated immune response and additional humoral immune response parameters to the Omicron XBB.1.5 strain will be summarized at each time point for the subset of participants with PBMC samples collected in each group.

10.8.9.4. Interim Analyses

No formal interim analysis will be conducted. As this is a sponsor–open-label study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in Section 10.8.9.4.1.

10.8.9.4.1. Analysis Timing

At a minimum, statistical analyses will be carried out when the following data are available:

- Safety and immunogenicity data through Visit B3 (1 month after study vaccination).
- Safety and immunogenicity data through Visit B5 (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.

10.8.9.5. Sample Size Determination

This substudy will enroll approximately 300 COVID-19 vaccine–naïve participants. The same number of vaccine-experienced participants will be selected from Substudy A as a control group to evaluate the immunogenicity primary objective. Assuming a 20%nonevaluable rate, approximately 240 evaluable participants in each group will contribute to the evaluation of the immunogenicity primary objective.

For comparisons based on GMR, common assay standard deviations at 1 month after the vaccination in log scale is assumed to be 1.35 based on data observed in Study C4591044. Table 11 provides the power to declare noninferiority under different assumptions of true GMRs of SARS-CoV-2 Omi XBB.1.5–neutralizing titers 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants in Substudy B to 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A, using 1.5-fold margin. If the true GMR is 1.0, the study will have 90.0% power to declare noninferiority. If the true GMR is 0.9, there is 66.6% power to declare noninferiority.

Table 11. Power to Demonstrate Noninferiority Under Different Assumptions of GMR

Number of Evaluable Participants in Each Group	Assumed True GMR	Power
240	1.0	90.0
240	0.9	66.6
240	0.8	30.0

Table 12 provides the power to demonstrate noninferiority under different assumptions of seroresponse rates for each comparative group, using a 10% margin. If the seroresponse rate is 80% in both comparator groups, the study will have 77.7% power to demonstrate noninferiority. If the seroresponse rate is 80% for vaccine-experienced participants in the Substudy A control group and 75% for vaccine-naïve participants in Substudy B, the study will have 25.9% power to demonstrate noninferiority.

Table 12. Power to Demonstrate Noninferiority Under Different Assumptions of Seroresponse Rate

Number of Evaluable Participants in Each Group	Assumed Seroresponse Rate in Substudy A Control Group (%)	Assumed Seroresponse Rate in Substudy B (%)	Power
240	80	80	77.7
240	80	75	25.9
240	70	70	66.8
240	70	65	21.7
240	60	60	61.2
240	60	55	19.9

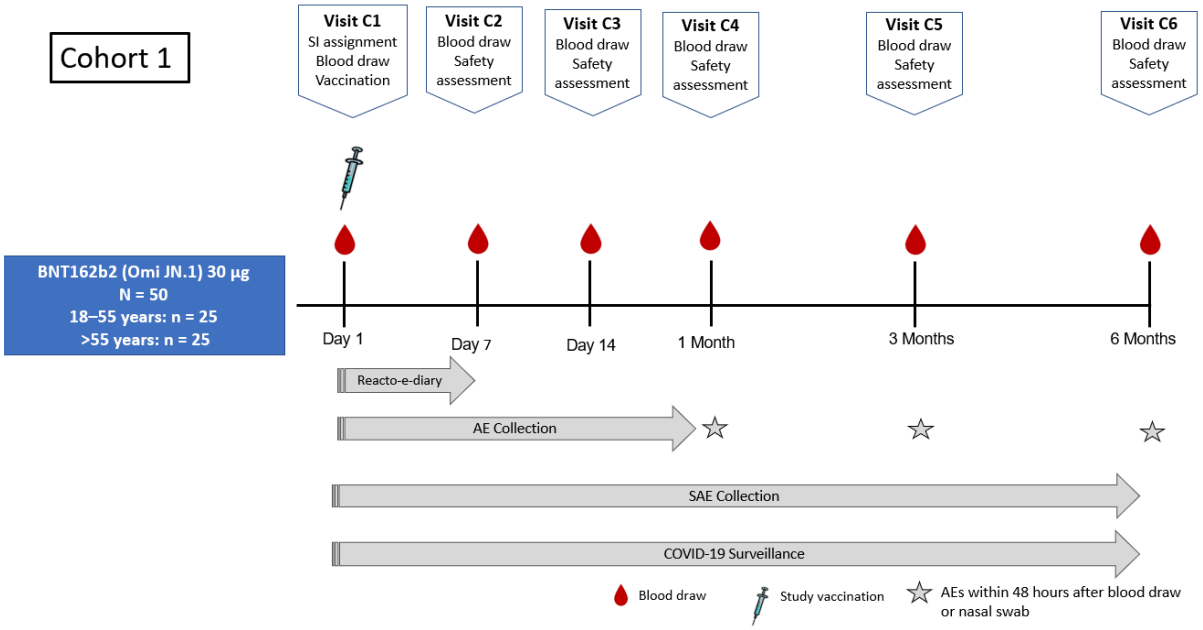
10.9. Appendix 9: Substudy C

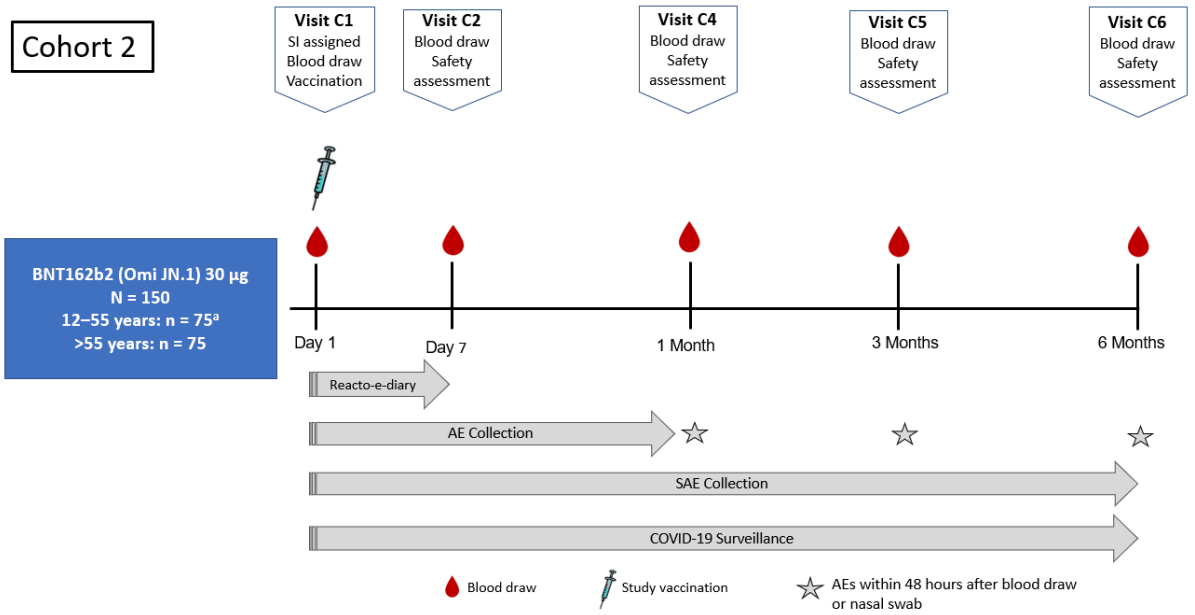
10.9.1. Substudy C Summary

10.9.1.1. Synopsis

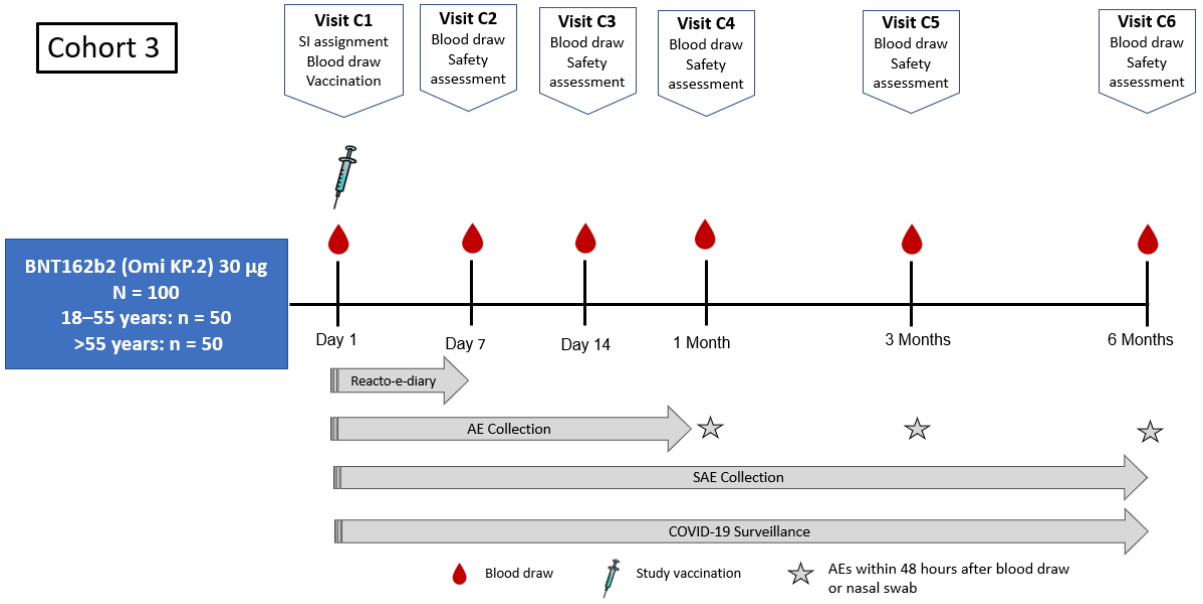
See Section 1.1 for the synopsis of Substudy C.

10.9.1.2. Schemas





a. A maximum of 20 participants 12 through 17 years of age will be enrolled. If fewer than 20 participants are enrolled in this age group, the difference will be added to the number of participants enrolled in the 18-through 55-year age group.



10.9.1.3. Schedule of Activities for Substudy C

Visit Identifier	C1	C2	C3	C4	C5	C6	Unplanned	Notes
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**2-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**	**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 10.9.8.5.9.
Visit Window	**Day 1**	**6 to 8 Days After Visit C1**	**12 to 16 Days After Visit C1**	**28 to 35 Days After Visit C1**	**84 to 98 Days After Visit C1**	**175 to 189 Days After Visit C1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	3-Month and 6-month visits may be performed as telehealth visits if the participant had blood draws discontinued.
			ONLY FOR COHORTS 1 and 3					
Obtain informed consent/assent	X							If vaccination is temporarily delayed, per Section 10.9.5.5, consent need not be obtained again on the day of vaccination. For participants <18 years of age (at the time of consent), the parent(s)/legal guardian will provide signed informed consent. Depending on the age of the participant and according to local requirements, participants will also be asked to provide assent as appropriate (verbal or written).
Assign participant number	X							If the participant is from a prior Pfizer COVID-19 study(ies), record the participant number(s) of the prior study(ies) in the CRF.
Obtain demography data	X							
Obtain authorization for and perform the participant verification process via third-party vendor, if applicable	X							Refer to Section 10.9.8.5.1 for details.

Visit Identifier	C1	C2	C3	C4	C5	C6	Unplanned	Notes
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**2-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**	**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 10.9.8.5.9.
Visit Window	**Day 1**	**6 to 8 Days After Visit C1**	**12 to 16 Days After Visit C1**	**28 to 35 Days After Visit C1**	**84 to 98 Days After Visit C1**	**175 to 189 Days After Visit C1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	3-Month and 6-month visits may be performed as telehealth visits if the participant had blood draws discontinued.
			ONLY FOR COHORTS 1 and 3					
Obtain medical history data (including confirmed COVID-19 diagnosis or asymptomatic positive SARS-CoV-2 test result)	X							
Record details of all prior COVID-19 vaccines (if applicable)	X							Record details in the prior COVID-19 vaccination CRF.
Urine pregnancy test (if appropriate)	X							Refer to Section 8.3.6.
Confirm use of contraceptives (if appropriate)	X	X	X	X				Refer to Section 5.3.1.
Measure height and weight	X							
Perform clinical assessment	X	X	X	X				Including, if indicated, a physical examination (Section 10.9.8.3.1).
Record nonstudy vaccine information	X	X	X	X	X	X	X	Refer to Section 10.9.6.9.
Record prohibited medication use		X	X	X	X	X	X	Refer to Section 10.9.6.9.1.
Confirm eligibility	X							Refer to Section 10.9.5.1 and Section 10.9.5.2.
Measure body temperature	X							
Review temporary delay criteria	X							See Section 10.9.5.5.
Obtain randomization number using the IRT system	X							Refer to Section 10.9.8.5.1.
Nasal (midturbinate) swab for SARS-CoV-2 NAAT	X						X	

Visit Identifier	C1	C2	C3	C4	C5	C6	Unplanned	Notes
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**2-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**	**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 10.9.8.5.9.
Visit Window	**Day 1**	**6 to 8 Days After Visit C1**	**12 to 16 Days After Visit C1**	**28 to 35 Days After Visit C1**	**84 to 98 Days After Visit C1**	**175 to 189 Days After Visit C1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	3-Month and 6-month visits may be performed as telehealth visits if the participant had blood draws discontinued.
			ONLY FOR COHORTS 1 and 3					
Blood sample for immunogenicity assessments	~50 mL / ~10 mL*	~20 mL / ~10 mL*	~20 mL	~50 mL / ~10 mL*	~20 mL / ~10 mL*	~20 mL / ~10 mL*		≥18-Year-olds: 50 mL/20 mL is to be collected. * 12-17-Year-olds: 10 mL is to be collected (Cohort 2 only). Blood sample collection may be halted or discontinued upon notification by Pfizer.
Blood sample for PBMC isolation – Cohort 2 and Cohort 3	~130 mL	~130 mL		~130 mL		~130 mL		Applicable at designated Cohort 2 and Cohort 3 sites only. Optional with additional consent given by participants ≥18 years of age. See Section 10.9.8.2.2.
Blood sample for HLA typing – Cohort 2 and Cohort 3	~5 mL							Applicable at designated Cohort 2 and Cohort 3 sites only. Optional with additional consent given by participants ≥18 years of age. See Section 10.9.8.2.2.
"Unblinded" staff obtains the participant's vaccine vial allocation using the IRT system	X							Refer to Section 10.9.8.5.1.
"Unblinded" staff administers study intervention	X							Refer to Section 6.1.1.

Visit Identifier	C1	C2	C3	C4	C5	C6	Unplanned	Notes
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**2-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**	**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 10.9.8.5.9.
Visit Window	**Day 1**	**6 to 8 Days After Visit C1**	**12 to 16 Days After Visit C1**	**28 to 35 Days After Visit C1**	**84 to 98 Days After Visit C1**	**175 to 189 Days After Visit C1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	3-Month and 6-month visits may be performed as telehealth visits if the participant had blood draws discontinued.
			ONLY FOR COHORTS 1 and 3					
Assess acute reactions (immediate events) for at least 30 minutes after study intervention administration	X							
Explain participant communication methods (including for potential COVID-19 illness and reactogenicity e-diary completion and severe reactogenicity symptoms), assist the participant with downloading the app or issue provisioned device, if required	X							
Provide thermometer and measuring device	X							
Provide/ensure participant has a self-swab kit in case of COVID-19 symptoms and instructions on self-collection of nasal swabs	X	X	X	X	X			
Ask/remind the participant to contact the site if the participant experiences any severe (Grade 3) reactogenicity symptoms	X	X						
Ask/remind the participant to contact the site if a medically attended event or hospitalization occurs	X	X	X	X	X			

Visit Identifier	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**Unplanned**	**Notes**
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**2-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**	**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 10.9.8.5.9.
Visit Window	**Day 1**	**6 to 8 Days After Visit C1**	**12 to 16 Days After Visit C1**	**28 to 35 Days After Visit C1**	**84 to 98 Days After Visit C1**	**175 to 189 Days After Visit C1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	3-Month and 6-month visits may be performed as telehealth visits if the participant had blood draws discontinued.
			ONLY FOR COHORTS 1 and 3					
Ask/remind the participant to contact the site immediately if the participant experiences any symptoms as detailed in Section 10.9.8.5.8 (COVID-19 or MIS-C)	X	X	X	X	X			
Participant completes COVID-19 illness e-diary		←	—	—	—	—	→	Refer to Section 10.9.8.3.4 and Section 10.9.8.5.8.
Ask/remind the participant to contact the site immediately if the participant experiences any symptoms of acute chest pain, shortness of breath, or palpitations	X	X	X	X				Report the specified cardiac illness symptoms through 42 days after study vaccination. Refer to Section 10.9.8.5.11.
Review of e-diary data with participant follow-up until ongoing symptom resolution	←	—	—	→				Daily review is optimal during the active diary period. E-diary data reviewed at Visits C2, C3 (Cohorts 1 and 3 only), and C4 with participant follow-up until ongoing symptom resolution (obtain stop dates). Assess compliance, record any medically attended events (including hospitalizations), and collect stop dates for any symptoms ongoing on the last day of the e-diary collection period (7 days) in the CRF.

Visit Identifier	C1	C2	C3	C4	C5	C6	Unplanned	Notes
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**2-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**	**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 10.9.8.5.9.
Visit Window	**Day 1**	**6 to 8 Days After Visit C1**	**12 to 16 Days After Visit C1**	**28 to 35 Days After Visit C1**	**84 to 98 Days After Visit C1**	**175 to 189 Days After Visit C1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	3-Month and 6-month visits may be performed as telehealth visits if the participant had blood draws discontinued.
			ONLY FOR COHORTS 1 and 3					
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	Includes nonserious AEs through Visit C4; any AEs occurring up to 48 hours after a blood draw or nasal swab collection; and SAEs or potential menstrual cycle disturbances through the end of the study (see Section 8.4.1 and Section 10.9.8.4.1).
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)							X	Refer to Section 10.9.8.2.1.
Assist the participant to delete the e-diary application or collect the provisioned device						X		

10.9.2. Introduction for Substudy C

10.9.2.1. Study Rationale

Global health authorities have recommended a monovalent Omicron JN.1 lineage vaccine (such as JN.1 and KP.2) for the 2024-2025 season, and as a result, Cohorts 1 and 2 will study the safety, tolerability, and immunogenicity of BNT162b2 (Omi JN.1) and Cohort 3 will study the safety, tolerability, and immunogenicity of BNT162b2 (Omi KP.2).

Cohort 1: Based on protocol amendment 1, this initial and smaller segment of the substudy is intended to enable Pfizer/BioNTech to obtain early safety, tolerability, and immunogenicity data for up to 2 BNT162b2-based vaccines, each targeting a predominant circulating variant of SARS-CoV-2 in anticipation of the recommendation for the 2024-2025 variant-adapted vaccine by global health authorities. With the implementation of protocol amendment 2, Cohort 1 will be limited to the evaluation of BNT162b2 (Omi JN.1).

Cohort 2: In this second and larger segment of the substudy, Pfizer/BioNTech will evaluate the safety, tolerability, and immunogenicity of BNT162b2 (Omi JN.1).

Cohort 3: In this segment of the substudy, Pfizer/BioNTech will evaluate the safety, tolerability, and immunogenicity of BNT162b2 (Omi KP.2).

All 3 cohorts will enroll individuals who are either COVID-19 vaccine naïve or experienced, to reflect a real-world population. In addition, there is no requirement for vaccine-naïve participants to have had a positive SARS-CoV-2 test, considering that most people have already been exposed to COVID-19.

Refer to Section 2.1 and Section 2.2 for further details on the rationale for this substudy.

10.9.2.2. Background

See Section 2.2 for the study background.

10.9.2.3. Benefits/Risk Assessment

No additional risks are identified for Substudy C beyond those detailed in Section 2.3.

10.9.2.4. Benefit Assessment

See Section 2.3.

10.9.3. Objectives, Estimands, and Endpoints for Substudy C

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
Safety		
Cohort 1 and Cohort 2 combined: To describe the safety and tolerability profile of BNT162b2 (Omi JN.1) 30 µg in participants ≥12 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 3: To describe the safety and tolerability profile of BNT162b2 (Omi KP.2) 30 µg in participants ≥18 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
Immunogenicity		
Cohort 1 and Cohort 2 combined: To describe the immune response to BNT162b2 (Omi JN.1) 30 µg and BNT162b2 (Omi XBB.1.5)[a] 30 µg in participants ≥12 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT 1 month after vaccination • GMFR from before the study vaccination to 1 month after vaccination • Percentages of participants with seroresponse[b] 1 month after vaccination	• SARS-CoV-2 Omi JN.1–neutralizing titers • SARS-CoV-2 Omi XBB.1.5–neutralizing titers
Cohort 3: To describe the immune response to BNT162b2 (Omi KP.2) 30 µg and BNT162b2 (Omi JN.1)[c] 30 µg in participants ≥18 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT 1 month after vaccination • GMFR from before the study vaccination to 1 month after vaccination • Percentages of participants with seroresponse[b] 1 month after vaccination	• SARS-CoV-2 Omi KP.2–neutralizing titers • SARS-CoV-2 Omi JN.1–neutralizing titers

Objectives	Estimands	Endpoints
Exploratory:	**Exploratory:**	**Exploratory:**
Cohort 1 and Cohort 2 combined: To describe the immune response to BNT162b2 Omi (JN.1)[d] 30 µg and BNT162b2 (Omi XBB.1.5)[a] 30 µg in participants ≥12 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point • GMFR from before the study vaccination to each subsequent time point • Percentages of participants with seroresponse[b] at each time point following vaccination for each variant-specific neutralizing titer	• SARS-CoV-2 Omi JN.1–neutralizing titers • SARS-CoV-2 Omi XBB.1.5–neutralizing titers
Cohort 3: To describe the immune response to BNT162b2 (Omi KP.2)[d] 30 µg and BNT162b2 (Omi JN.1)[c] 30 µg in participants ≥18 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point • GMFR from before the study vaccination to each subsequent time point • Percentages of participants with seroresponse[b] at each time point following vaccination for each variant-specific neutralizing titer	• SARS-CoV-2 Omi KP.2–neutralizing titers • SARS-CoV-2 Omi JN.1–neutralizing titers
Cohort 1 and Cohort 2 combined: To describe confirmed COVID-19 and severe COVID-19 cases.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
Cohort 3: To describe confirmed COVID-19 and severe COVID-19 cases.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
Cohort 1 and Cohort 2 combined: To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern).[d]		• SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified
Cohort 3: To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern).[d]		• SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified

Objectives	Estimands	Endpoints
Cohort 2: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the Omicron JN.1 strain in a subset of participants ≥18 years of age with PBMC samples collected.		
Cohort 3: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the Omicron KP.2 strain in a subset of participants with PBMC samples collected.		

a. The participants from Substudy A will be used as a historical control for this objective, for the matched time points.
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. The participants from Substudy C, Cohorts 1 and 2 combined, will be used as a historical control.
d. Immunogenicity samples from a subset of participants may be tested for this objective.

10.9.4. Study Design for Substudy C

10.9.4.1. Overall Study Design

This is a Phase 2/3 open-label study to evaluate the safety, tolerability, and immunogenicity of 2 BNT162b2-based vaccines, each targeting a predominant circulating variant of SARS-CoV-2. The substudy will be divided into 3 cohorts.

Cohort 1 will enroll approximately 50 participants 18 years of age and older (approximately 25 participants each in the 18- through 55-year and >55-year age groups), who will receive a single 30-µg dose of BNT162b2 (Omi JN.1). The study duration will be approximately 6 months, with 6 scheduled visits. Reactogenicity e-diaries will be used to collect prespecified local reaction and systemic event data during the 7-day collection period, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution). The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity.

Participants from Study C4591054 – Substudy A who received BNT162b2 (Omi XBB.1.5) 30 µg will be used as a control group for immunogenicity, for the matched time points.

Table 13. Substudy C Design: Cohort 1

Open-Label				
Group	**Study Intervention**	**Study Dose**	**Participant Age Group**	**Number of Participants**
1	BNT162b2 (Omi JN.1)	30 µg	18-55 Years	25
			>55 Years	25

Cohort 2 will enroll participants ≥12 years of age who will receive a single open-label 30-µg dose of BNT162b2 (Omi JN.1). Enrollment into Cohort 2 will begin once Cohort 1 has completed enrollment. Approximately 150 participants will be enrolled into Cohort 2, resulting in a total of 200 participants receiving BNT162b2 (Omi JN.1) (including the 50 participants from Cohort 1). The study duration will be approximately 6 months, with 5 scheduled visits (no 2-week visit). Reactogenicity e-diaries will be used to collect prespecified local reaction and systemic event data during the 7-day collection period, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution). The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 30 participants each in the 18- through 55-year and >55-year age groups who consent to collection of optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing.

For both cohorts, participants from Study C4591054 – Substudy A who received BNT162b2 (Omi XBB.1.5) 30 µg will be used as a control group for immunogenicity assessment (for the matched time points).

Table 14. Substudy C Design: Cohort 2

Open-Label				
Group	**Study Intervention**	**Study Dose**	**Participant Age Group**	**Number of Participants**
1	BNT162b2 (Omi JN.1)	30 µg	12-55 Years	75[a]
			>55 Years	75

a. A maximum of 20 participants 12 through 17 years of age will be enrolled. If fewer than 20 participants are enrolled in this age group, the difference will be added to the number of participants enrolled in the 18-through 55-year age group.

Cohort 3 will enroll participants ≥18 years of age who will receive a single open-label 30-µg dose of BNT162b2 (Omi KP.2), which targets the SARS-CoV-2 variant Omicron KP.2. Approximately 100 participants will be enrolled. The study duration will be approximately 6 months, with 6 scheduled visits. Reactogenicity e-diaries will be used to collect prespecified local reaction and systemic event data during the 7-day collection period, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution). The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 20 participants each in the 18- through 55-year and >55-year age groups who consent to collection of optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing.

Participants from Study C4591054 – Substudy C, Cohorts 1 and 2 combined, who received BNT162b2 (Omi JN.1) 30 µg will be used as a control group for immunogenicity assessment of BNT162b2 (Omi KP.2).

Table 15. Substudy C Design: Cohort 3

Open-Label				
Group	**Study Intervention**	**Study Dose**	**Participant Age Group**	**Number of Participants**
1	BNT162b2 (Omi KP.2)	30 µg	18-55 Years	50
			>55 Years	50

All cohorts will enroll participants who are either COVID-19 vaccine naïve or experienced. Those who have received prior COVID-19 vaccine(s) must have received the most recent dose at least 150 days prior to study vaccination (Visit C1/Day 1).

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

10.9.4.2. Scientific Rationale for Substudy C Design

See Section 10.9.2.1.

10.9.4.3. Rationale for Comparator

For both Cohorts 1 and 2, Substudy A participants will be used as a historical comparator for immunogenicity for the matched time points. All Substudy A participants received BNT162b2 (Omi XBB.1.5) 30 µg as fourth or higher dose. This is the vaccine authorized for the 2023-2024 season and administered to individuals in the US since 11 September 2023.[57] For Cohort 3, both JN.1 and KP.2 have been recommended as variant-adapted vaccines for the 2024-2025 season, therefore, Substudy C Cohorts 1 and 2, combined, will be used as a historical comparator for immunogenicity evaluation of BNT162b2 (Omi KP.2). All Cohort 1 and Cohort 2 participants will have received BNT162b2 (Omi JN.1) 30 µg.

10.9.4.4. Justification of Dose

Refer to Section 4.5 for justification of the 30-µg dose level.

10.9.4.5. End of Study Definition

See Section 4.6.

10.9.5. Study Population for Substudy C

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.

10.9.5.1. Inclusion Criteria

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

Age and Sex:

1. At Visit C1 (Day 1):
    - Cohort 1: Participants ≥18 years of age.
    - Cohort 2: Participants ≥12 years of age.
    - Cohort 3: Participants ≥18 years of age.

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 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 or have parent(s)/legal guardian capable of giving signed informed consent 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 (as defined in Appendix 1, Section 10.1.3), and the participant's assent, when applicable, before any study-specific activity is performed. All 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 document.

10.9.5.2. Exclusion Criteria

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

6. History of myocarditis or pericarditis.

Prior/Concomitant Therapy:

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

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

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

9. Receipt of a COVID-19 vaccine less than 150 days before Visit C1 (Day 1).

Prior/Concurrent Clinical Study Experience:

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

Other Exclusion Criteria:

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

10.9.5.3. Lifestyle Considerations

10.9.5.3.1. Contraception

See Section 5.3.1.

10.9.5.4. Screen Failures

See Section 5.4.

10.9.5.5. 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 C1 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 10.9.8.2.1).

   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 on a local test 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 at a dose of ≥20 mg/day of prednisone or equivalent. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days.

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

10.9.6. Study Interventions and Concomitant Therapy for Substudy C

10.9.6.1. Study Intervention Administered

For the purposes of this substudy, study intervention refers to the following.

Cohort 1

- BNT162b2 (Omi JN.1) =

  BNT162b2 Omicron (B.1.1.529) sublineage JN.1

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

Study Intervention – Substudy C, Cohort 1	
Intervention Name	BNT162b2 (Omi JN.1) (BNT162b2 monovalent [Omicron JN.1]) Preformulated as a single vial (no dilution required)
Type	Vaccine
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	modRNA
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg
Route of Administration	Intramuscular injection
Sourcing	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in single-dose glass vials as open-label supply. Vials will be labeled as required per country requirement.
SRSD	IB

Study Arm – Substudy C, Cohort 1	
Arm Title	BNT162b2 (Omi JN.1) 18-55 years and >55 years
Arm Description	Participants will receive BNT162b2 (Omi JN.1) 30 µg at Visit C1

Study Intervention - Substudy C, Cohort 2	
Intervention Name	BNT162b2 (Omi JN.1) (BNT162b2 monovalent [Omicron JN.1]) Preformulated as a single vial (no dilution required)
Type	Vaccine
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	modRNA
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg
Route of Administration	Intramuscular injection
Sourcing	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in single-dose glass vials as open-label supply. Vials will be labeled as required per country requirement.
SRSD	IB

Study Arm - Substudy C, Cohort 2	
Arm Title	BNT162b2 (Omi JN.1) 12-55 years and >55 years
Arm Description	Participants will receive BNT162b2 (Omi JN.1) 30 µg at Visit C1.

Study Intervention - Substudy C, Cohort 3	
Intervention Name	BNT162b2 (Omi KP.2) (BNT162b2 monovalent [Omicron KP.2]) Preformulated as a single vial (no dilution required)
Type	Vaccine
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	modRNA
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg
Route of Administration	Intramuscular injection
Sourcing	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in single-dose glass vials as open-label supply. Vials will be labeled as required per country requirement.
SRSD	IB

Study Arm - Substudy C, Cohort 3	
Arm Title	BNT162b2 (Omi KP.2) 18-55 years and >55 years
Arm Description	Participants will receive BNT162b2 (Omi KP.2) 30 µg at Visit C1.

10.9.6.1.1. Administration

Cohort 1: Participants will receive 1 dose of BNT162b2 (Omi JN.1) at Visit C1 in accordance with the study's SoA.

Cohort 2: Participants will receive 1 dose of BNT162b2 (Omi JN.1) at Visit C1 in accordance with the study's SoA.

Cohort 3: Participants will receive 1 dose of BNT162b2 (Omi KP.2) at Visit C1 in accordance with the study's SoA.

For other details regarding study intervention administration, see Section 6.1.1.

10.9.6.2. Preparation, Handling, Storage, and Accountability

See Section 6.2.

10.9.6.3. Assignment to Study Intervention

See Section 6.3.

10.9.6.4. Blinding

Cohorts 1, 2, and 3 will be open-label.

10.9.6.4.1. Blinding of Participants

Participants will not be blinded to study intervention.

10.9.6.4.2. Blinding of Site Personnel

Investigators and other site staff will not be blinded to participants' assigned study intervention. However, the IRT system for this protocol is set up to accommodate multiple substudies, some of which may be observer-blind studies. Therefore, to maintain consistency across substudies, study staff assigned to the "unblinded" role, per the delegation log, will receive, store, assign, and prepare the study intervention and are considered "unblinded" study staff. The study-specific IRT reference manual and IPM provide further details.

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

10.9.6.4.3. Blinding of the Sponsor

The majority of Pfizer staff will be unblinded to the study intervention assigned/received. All laboratory testing personnel performing serology assays where a comparator group is also analyzed will remain blinded to study intervention assigned/received. All laboratory personnel performing serology and PCR testing will be blinded to the participant's identity, study visit, or study cohort associated with the sample.

10.9.6.4.4. Breaking the Blind

Not applicable.

10.9.6.5. Study Intervention Compliance

See Section 6.5.

10.9.6.6. Dose Modification

See Section 6.6.

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

See Section 6.7.

10.9.6.8. Treatment of Overdose

See Section 6.8.

10.9.6.9. Prior and Concomitant Therapy

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

- Prohibited medications listed in Section 10.9.6.9.1 will be recorded in the concomitant medication CRF.
- 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.

10.9.6.9.1. 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.

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after the study vaccination, with the exception of seasonal and pandemic influenza vaccine, which 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.

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

- Receipt of short-term (<14 days) systemic corticosteroids at a dose of ≥20 mg/day of prednisone or equivalent is prohibited from 28 days prior to enrollment 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.

10.9.6.9.2. Permitted During the Study

Medication other than that described as prohibited in Section 10.9.6.9.1 required for treatment of preexisting conditions, acute illness, or to treat symptoms associated with study intervention administration is permitted.

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

- Systemic corticosteroids administered at a dose of <20 mg/day of prednisone or equivalent are permitted.

10.9.7. Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal for Substudy C

See Section 7.1 and Section 7.2.

10.9.8. Study Assessments and Procedures for Substudy C

10.9.8.1. Administrative Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD from the participant or the participant's parent(s)/legal guardian, and the participant's assent (when applicable), before performing any study-specific procedures.

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.

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

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

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

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

10.9.8.1.1. Baseline Procedures

The baseline procedures are listed below. They are performed at Visit C1 (Day 1):

- Record demography data (including age in years, sex, race, and ethnicity). The age will be collected to critically evaluate the immune response and safety profile and to identify pediatric participants.

- 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.

10.9.8.1.2. Telehealth Visits

- Potential COVID-19 illness visits may be conducted as telehealth visits. Refer to Section 10.9.8.5.9.

- Any participants who have scheduled blood draws discontinued* may be followed for safety at Visit C5 (Month 3) and Visit C6 (Month 6) via telehealth visits. Note: Visit C1 (Day 1), Visit C2 (Week 1), Visit C3 (Week 2 – Cohort 1 only), and Visit C4 (Month 1) must remain as in-person visits to the site.

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

General requirements:

- Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Assessments that may be performed during a telehealth visit are described in the SoA. Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.

- If applicable: Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- If applicable: Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 10.4.

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

10.9.8.2. Efficacy and/or Immunogenicity Assessments

10.9.8.2.1. Surveillance for COVID-19 and MIS-C

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 10.9.8.5.8), for the purposes of the study he or she will be considered to potentially have COVID-19. In this circumstance, the participant 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 10.9.8.5.9) 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 to be 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;
    - 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. 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, deemed necessary.
- **Confirmed severe COVID-19 (FDA definition)[54]:** 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)**[55]**:** confirmed COVID-19 and presence of at least 1 of the following:
  - Hospitalization;
  - Admission to the ICU;
  - Intubation or mechanical ventilation;
  - Death.

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[56]:

- 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.

10.9.8.2.2. Vaccine-Induced Immunogenicity

Blood samples will be obtained for immunogenicity testing at the central laboratory.

The SARS-CoV-2 neutralization assay will be run on serum samples obtained for the following variants:

- Omicron JN.1
- Omicron KP.2
- Omicron XBB.1.5

At designated sites, optional whole blood samples of ~130 mL for isolation of PBMCs will be obtained from up to approximately 30 Cohort 2 participants per adult age group (18-55 and >55 years) and from approximately 20 Cohort 3 participants in each age group (18-55 and >55 years) for evaluation of boostability (in COVID-19 vaccine–experienced participants) and protection against the variant strain. These samples will be used to describe B-cell and T-cell responses to the variant and the original strains. A blood sample of ~5 mL for HLA typing will also be obtained (at Visit C1 only). Refer to the SoA for time points of collection.

10.9.8.2.3. N-Binding Antibody Test

The N-binding antibody test will be performed by the central laboratory at certain blood sample collections to establish prior exposure to SARS-CoV-2 up to the time point. These data will be used for study analyses.

10.9.8.2.4. Biological Samples

Refer to Section 8.2.4 for general information regarding use and storage of biological samples.

The total blood sampling volume for individual participants at scheduled visits in this study is approximately 180 mL for participants in Cohort 1, 50 mL for participants 12 through 17 years of age in Cohort 2, 160 mL for participants ≥18 years of age in Cohort 2, and 180 mL for participants in Cohort 3. Those participants ≥18 years of age in Cohort 2 and Cohort 3 participants who consent to additional blood collection for isolation of PBMCs and additional serology will have a total blood sampling volume of up to approximately 685 mL and 705 mL, respectively. 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.

Blood sample collection may be halted or discontinued upon notification by Pfizer. This includes discontinuing sampling in dosed participants who are no longer eligible for the study as well as discontinuation for groups of participants or all participants.

10.9.8.3. 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.

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

10.9.8.3.2. Vital Signs

The participant's body temperature will be measured 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 Sections 8.4.1 to 8.4.3.

10.9.8.3.3. Clinical Safety Laboratory Assessments

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

10.9.8.3.4. Electronic Diary

E-diary assessments are included in Substudy C for participants' reporting of local reactions and systemic events for 7 days from the day of administration of the study intervention. Participants will receive reminders to complete the vaccination e-diary on a daily basis, starting on the day of vaccination (Day 1) until symptoms are reported as resolved. Refer to Section 8.3.5 for details.

The e-diary is also 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 diary on a weekly basis throughout the study and whenever they receive a diagnosis of COVID-19 or experience symptoms of COVID-19. Refer to Section 10.9.8.5.7 for details.

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

Refer to Section 8.4 and the following subsections:

- Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information
- Section 8.4.2 Methods of Detecting AEs and SAEs
- Section 8.4.3 Follow-Up of AEs and SAEs
- Section 8.4.4 Regulatory Reporting Requirements for SAEs
- Section 8.4.5 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure
- Section 8.4.6 Cardiovascular and Death Events
- Section 8.4.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs
- Section 8.4.9Medical Device Deficiencies
- Section 8.4.10 Vaccination Errors

10.9.8.4.1. Adverse Events of Special Interest

The following events, if reported, have additional procedures associated with their evaluation; they are, therefore, considered protocol-specified AESIs:

- Confirmed diagnosis of myocarditis or pericarditis occurring within 6 weeks after vaccination. See Section 10.9.8.5.11.
- Potential menstrual cycle disturbances occurring within 6 months after vaccination. See Section 10.9.8.5.12.

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

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

10.9.8.4.1.1. 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**.

10.9.8.4.2. Genetics

Refer to Section 8.6.

10.9.8.5. Substudy C Procedures

10.9.8.5.1. Visit C1 – Study Intervention Administration – Day 1

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian as appropriate, and assent will be obtained from the participant, if appropriate. 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 or his/her parent(s)/legal guardian as appropriate. 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 number of both the most recent prior study and the first study in the CRF.

- Obtain the participant's demography (including age in years, sex, race, and ethnicity).

- Obtain authorization from the participant and perform the participant verification process, if applicable, via the third-party vendor. This process helps ensure Pfizer clinical data quality and participant safety on trials by aiding investigational sites in the monitoring for and halting of dual enrollment of participants. The participant must sign the authorization form before the verification process is initiated. Refer to the vendor's research site manual for details.

- 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.

- If applicable, review all/any prior COVID-19 vaccinations with participant. The most recent dose must have been administered at least 150 days before Visit C1/Day 1, to meet eligibility criteria, as specified in Section 10.9.5.2, exclusion criterion 9.
- Perform a urine pregnancy test on WOCBP as described in Section 8.3.6.
- 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 10.9.8.3.1), 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 10.9.6.9.
- 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.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 10.9.5.5.
- Site staff will obtain the participant's randomization number using the IRT system and will receive the randomization confirmation report.
- 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 10 mL for participants 12 through 17 years of age and approximately 50 mL for participants ≥18 years of age) for testing of immunogenicity and N-binding antibody.
- Cohort 2 and Cohort 3: If the participant is part of the group for description of cell-mediated and additional humoral immune responses (select sites only; ≥18 years of age only; additional consent required),
  - collect a blood sample (approximately 130 mL) for PBMC isolation,
  - collect an additional blood sample of approximately 5 mL for HLA typing.
- 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 the "unblinded" site staff role.

- A site staff member assigned to the "unblinded" role, per the delegation log, 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.

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

- Record AEs as described in Section 8.4.

- Explain the e-diary technologies available for this study (see Section 8.3.5) and assist the participant or his/her parent(s)/legal guardian in downloading the study application onto the participant's own device or issue a provisioned device if required.

- Provide instructions on e-diary completion and ask the participant or his/her parent(s)/legal guardian to complete the reactogenicity e-diary from Day 1 through Day 7, or longer until symptoms that are ongoing are resolved, with Day 1 being the day of vaccination (see Section 8.3.5 through Section 8.3.5.4).

- Remind the participant that study staff may contact them to obtain information on symptoms entered into the e-diary until they resolve.

- 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.

- Ask the participant or his/her 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.

  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator to report any significant illness (new or worsening), medically attended event (eg, doctor's visit, emergency room visit), or hospitalization that occurs during the study.

- Provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her 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 10.9.8.5.8 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.

- 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 10.9.8.5.11).

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

- Remind the participant or his/her 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 a dispenser/administrator updates the study intervention accountability records.

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

10.9.8.5.2. Visit C2 – 1-Week Follow-Up Visit (6 to 8 Days After Visit A1)

- 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 10.9.6.9.

- Record details of any of the prohibited medications specified in Section 10.9.6.9.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 5.3.1.

- Collect a blood sample (approximately 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 20 mL for participants ≥18 years of age) for immunogenicity testing.

- Cohort 2 and Cohort 3: If the participant is part of the group for description of cell-mediated immune response (select sites only; ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.

- If the 7-day reactogenicity period is still ongoing: Remind the participant to complete the reactogenicity e-diary from Day 1 through Day 7, or longer, until any symptoms that are ongoing are resolved, with Day 1 being the day of vaccination (see Section 8.3.5 through Section 8.3.5.4).

- If the 7-day reactogenicity period is still ongoing: Remind the participant or his/her 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.

  - Any severe systemic event.

- If the 7-day reactogenicity period has ended: Review the participant's reactogenicity e-diary data and record the assessment in the CRF. Assess compliance, record any medically attended events (including hospitalization), and collect stop dates for any symptoms ongoing on the last day of the e-diary collection period in the CRF. For symptoms still ongoing, continue to follow up until resolution, and document and record stop dates in the CRF.

- Remind the participant that study staff may contact them to obtain information on symptoms entered into the e-diary until they resolve.

- Record AEs as described in Section 8.4.

- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator to report any significant illness (new or worsening), medically attended event (eg, doctor's visit, emergency room visit), or hospitalization that occurs during the study.

- 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 10.9.8.5.11).

- Ask the participant or his/her 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 10.9.8.5.8.

- Ensure that the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.

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

10.9.8.5.3. Visit C3 – 2-Week Follow-Up Visit (12-16 Days After Visit C1) – Cohort 1 and Cohort 3

- 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 10.9.6.9.

- Record details of any of the prohibited medications specified in Section 10.9.6.9.1 received by the participant if required for his or her clinical care.

- Confirm contraceptive use as described in Section 5.3.1.

- Collect a blood sample of approximately 20 mL for immunogenicity testing.

- Review the participant's reactogenicity e-diary data and record the assessment in the CRF. Assess compliance, record any medically attended events (including hospitalization), and collect stop dates for any symptoms ongoing on the last day of the e-diary collection period in the CRF. For symptoms still ongoing, continue to follow up until resolution, and document and record stop dates in the CRF.

- Remind the participant that study staff may contact them to obtain information on symptoms entered into the e-diary until they resolve.

- Record AEs as described in Section 8.4.

- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator to report any significant illness (new or worsening), medically attended event (eg, doctor's visit, emergency room visit), or hospitalization that occurs during the study.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.9.8.5.11).

- Ask the participant 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 10.9.8.5.8.

- Ensure that the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.

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

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

10.9.8.5.4. Visit C4 – 1-Month Follow-Up Visit (28-35 Days After Visit C1)

- 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 10.9.6.9.

- Record details of any of the prohibited medications specified in Section 10.9.6.9.1 received by the participant if required for his or her clinical care.

- Confirm contraceptive use as described in Section 5.3.1.

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

- Cohort 2 and Cohort 3: If the participant is part of the group for description of cell-mediated immune response (select sites only; ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.

- Cohort 2 only: Review the participant's reactogenicity e-diary data and record the assessment in the CRF. Assess compliance, record any medically attended events (including hospitalization), and collect stop dates for any symptoms ongoing on the last day of the e-diary collection period in the CRF.

- If the participant still has ongoing reactogenicity symptoms, continue to follow up until resolution, and document and record stop dates in the CRF.

- Remind the participant that study staff may contact them to obtain information on symptoms entered into the e-diary until they resolve.

- Record AEs as described in Section 8.4.
- Remind the participant or his/her 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 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 10.9.8.5.11).
- Ask the participant or his/her 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 10.9.8.5.8.
- Ensure that the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.9.8.5.5. Visit C5 – 3-Month Follow-Up Visit (84-98 Days After Visit C1)

- Record nonstudy vaccinations as described in Section 10.9.6.9.
- Record details of any of the prohibited medications specified in Section 10.9.6.9.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 20 mL for participants ≥18 years of age) for immunogenicity testing, unless advised otherwise by Pfizer.
- Record SAEs (and any AEs occurring within 48 hours of blood draw or nasal swab collection) as described in Section 8.4.
- Remind the participant or his/her 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 his/her 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 10.9.8.5.8.

- Ensure that the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.9.8.5.6. Visit C6 – 6-Month Follow-Up Visit (175-189 Days After Visit C1)

- Record nonstudy vaccinations as described in Section 10.9.6.9.
- Record details of any of the prohibited medications specified in Section 10.9.6.9.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 10 mL for participants 12 through 17 years of age at the time of consent, and approximately 20 mL for participants ≥18 years of age) for immunogenicity testing, unless advised otherwise by Pfizer.
- Cohort 2 and Cohort 3: If the participant is part of the group for description of cell-mediated immune response (select sites only; ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.
- Record AESIs and SAEs (and any AEs occurring within 48 hours of blood draw or nasal swab collection) as described in Section 8.4.
- Collect the participant's e-diary provisioned device or assist the participant or his/her 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.

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

If a Grade 3 local reaction (Section 8.3.5.2), systemic event (Section 8.3.5.3), or fever (Section 8.3.5.4) is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated.

This includes:

- redness at the injection site measuring >20 measuring device units (>10.0 cm),
- swelling at the injection site measuring >20 measuring device units (>10.0 cm),

- severe injection site pain,
- fever ≥39.0°C (≥102.1°F),
- any severe systemic event.

If a suspected Grade 4 local reaction (Section 8.3.5.2), systemic event (Section 8.3.5.3), or fever >40.0°C (>104.0°F) (Section 8.3.5.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless:

- The participant is unable to attend the unscheduled visit, or
- The local reaction/systemic event is no longer present at the time of the telephone contact, or
- The participant or his/her parent(s)/legal guardian recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error), or
- The investigator or authorized designee determined that the visit was not required, or
- The investigator or authorized designee confirmed severe reactogenicity assessment via medical records and/or telehealth assessment.

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.

10.9.8.5.8. COVID-19 and MIS-C Surveillance

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), the participant or his/her parent(s)/legal guardian is instructed to contact the site immediately. If confirmed to be a potential COVID-19 illness, the site should schedule and conduct either an in-person or telehealth visit as soon as possible, optimally within 3 days after symptom onset (and at the latest 4 days after symptom resolution). Refer to Section 10.9.8.2.1 for more details on COVID-19 and MIS-C surveillance.

- 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. 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, deemed necessary.
- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered to be 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 the vaccination, 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 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 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 as a potential COVID-19 illness; if not, the symptoms that overlap with systemic events should be recorded in the reactogenicity e-diary or as AEs, if not captured in the reactogenicity e-diary.

The participant or his/her parent(s)/legal guardian is 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.

The participant or his/her parent(s)/legal guardian may utilize a COVID-19 illness e-diary through an application (see Section 10.9.8.3.4) installed on a provisioned device or on the participant's or his/her 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, the participant or his/her parent(s)/legal guardian should be encouraged to seek care, if appropriate, from the participant's usual provider.

10.9.8.5.9. 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, videoconferencing software) remotely, thus allowing the participant 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 10.9.6.9.1 received by the participant if required for his or her clinical care.
- Record nonstudy vaccinations as described in Section 10.9.6.9.
- Record AEs as described in Section 8.4. Note: Potential COVID-19/MIS-C illnesses with their sequelae 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 or his/her parent(s)/legal guardian to self-collect a nasal (midturbinate) swab at home and ship it for assessment at the central laboratory.
- 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.

  - 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, computed tomography 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.

10.9.8.5.10. SARS-CoV-2 NAAT Results

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

- Visit C1: 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.

Research laboratory–generated positive results from the vaccination visit swabs, and all results from the illness visit swabs, will be provided to the site at the end of the study and, therefore, cannot be relied upon to direct clinical care. The participant or his/her parent(s)/legal guardian should be directed to seek additional testing through the participant's primary healthcare provider at a licensed clinical laboratory when the participant is exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing, as per local guidance.

10.9.8.5.11. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports the following within 6 weeks after the study vaccination:

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

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 and Section 8.4.3). Other diagnoses should be recorded as AEs or SAEs, as appropriate. Refer also to Section 10.9.8.4.1.

10.9.8.5.12. Additional Procedures for Monitoring of Potential Menstrual Cycle Disturbances

Any female study participant who reports any symptoms that may indicate a disturbance of their normal menstrual bleeding (eg, heavy menstrual bleeding, amenorrhea, irregular periods) following receipt of study intervention until 6 months after vaccination should be specifically evaluated by the investigator. Details of the symptoms, menstrual history, and results of any investigations performed will be recorded in the designated CRF. In addition, the potential disturbances must be reported as AEs, or SAEs, as appropriate.

10.9.8.5.13. Communication and Use of Technology

In a study of this nature that requires events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant 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, 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 8.3.5.
- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary) – see Section 10.9.8.5.8.
- If a participant or his/her parent(s)/legal guardian 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 to ascertain why and also to obtain details of any missed events.
- Messages of thanks and encouragement from the study team.

10.9.9. Statistical Considerations for Substudy C

See Section 9 for general protocol statistical considerations and see specific Substudy C statistical considerations below.

10.9.9.1. Statistical Hypotheses

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

10.9.9.1.1. Estimands

The estimands corresponding to the primary objectives are described in the table in Section 10.9.3.

The safety primary objective evaluations are based on the safety population. In general, completely missing reactogenicity data (ie, all 7 days of collection were missing) will not be imputed. For partially 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 objective are based on the evaluable immunogenicity population (Section 10.9.9.2). 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.

10.9.9.1.2. Multiplicity Adjustment

No multiplicity adjustment is needed for the study, as there is no statistical hypothesis.

10.9.9.2. Analysis Sets

For the purpose of analysis, in addition to the analysis sets defined in Section 9.2, the following analysis sets are defined for this substudy:

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

10.9.9.3. 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 substudy endpoints.

10.9.9.3.1. General Considerations

Refer to Section 9.3.1 for general considerations of statistical analyses.

10.9.9.3.2. Primary Endpoints/Estimands Analysis

Endpoint	Statistical Analysis Methods
Safety	Cohort 1 and Cohort 2 combined, Cohort 3: Descriptive statistics will be provided for each reactogenicity endpoint by age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall. 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

Endpoint	Statistical Analysis Methods
	percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs from the study vaccination through 1 month and SAEs from the study vaccination through 6 months after the study vaccination will be provided by age subgroup and overall.
Immunogenicity	Cohort 1 and Cohort 2 combined: For each vaccine group, the BNT162b2 (Omi JN.1) 30-µg group in this substudy and the historical control of BNT162b2 (Omi XBB.1.5) 30-µg group from Substudy A, • GMTs and 2-sided 95% CIs of SARS-CoV-2 Omi JN.1–neutralizing titers and SARS-CoV-2 Omi XBB.1.5–neutralizing titers at 1 month after study vaccination will be provided for each age subgroup and overall. Statistical methods are described in Section 9.3.1.2.1. • GMFRs of SARS-CoV-2 Omi JN.1–neutralizing titers and SARS-CoV-2 Omi XBB.1.5–neutralizing titers from baseline (before the study vaccination) to 1 month after study vaccination, along with the associated 2-sided 95% CIs, will be provided for each age subgroup and overall. Statistical methods are described in Section 9.3.1.2.3. • The percentages of participants with seroresponse to SARS-CoV-2 Omi JN.1 and SARS-CoV-2 Omi XBB.1.5 at 1 month after vaccination and the associated Clopper-Pearson 95% CIs will be provided for each age subgroup and overall. • The above analysis may be performed by baseline SARS-CoV-2 infection status if there is a sufficient number of participants without prior SARS-CoV-2 infection. • The above analysis may be performed by prior Covid vaccine history at baseline (naïve or experienced) if there is a sufficient number of participants in both of these categories.

Endpoint	Statistical Analysis Methods
	Cohort 3: For each vaccine group, the BNT162b2 (Omi KP.2) 30-µg group in Cohort 3 and the historical control of BNT162b2 (Omi JN.1) 30-µg group in Cohorts 1 and 2 combined, • GMTs and 2-sided 95% CIs of SARS-CoV-2 Omi KP.2–neutralizing titers and SARS-CoV-2 Omi JN.1–neutralizing titers at 1 month after study vaccination will be provided for each age subgroup and overall. Statistical methods are described in Section 9.3.1.2.1. • GMFRs of SARS-CoV-2 Omi KP.2–neutralizing titers and SARS-CoV-2 Omi JN.1–neutralizing titers from baseline (before the study vaccination) to 1 month after study vaccination, along with the associated 2-sided 95% CIs, will be provided for each age subgroup and overall. Statistical methods are described in Section 9.3.1.2.3. • The percentages of participants with seroresponse to SARS-CoV-2 Omi KP.2 and SARS-CoV-2 Omi JN.1 at 1 month after vaccination, and the associated Clopper-Pearson 95% Cis, will be provided for each age subgroup and overall. • The above analysis may be performed by baseline SARS-CoV-2 infection status if there is a sufficient number of participants without prior SARS-CoV-2 infection. • The above analysis may be performed by prior Covid vaccine history at baseline (naïve or experienced) if there is a sufficient number of participants in both of these categories.

10.9.9.3.3. Exploratory Endpoints Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	Cohort 1 and Cohort 2 combined: For each vaccine group, the BNT162b2 (Omi JN.1) 30-µg group in this substudy and the historical control of BNT162b2 (Omi XBB.1.5) 30-µg group from Substudy A, • GMTs, GMFRs, and percentages of participants with seroresponse to SARS-CoV-2 (Omi JN.1) and SARS-CoV-2 Omi XBB.1.5 at each time point, along with the associated 95% CIs, will be summarized in the same way as for the immunogenicity primary endpoints described above. This analysis may be conducted in a selected subset of participants. Cohort 3: For each vaccine group, the BNT162b2 (Omi KP.2) 30-µg group in Cohort 3 and the historical control of BNT162b2 (Omi JN.1) 30-µg group in Cohorts 1 and 2 combined, • GMTs, GMFRs, and percentages of participants with seroresponse to SARS-CoV-2 (Omi KP.2) and SARS-CoV-2 Omi JN.1 at each time point, along with the associated 95% CIs, will be summarized in the same way as for the immunogenicity primary endpoints described above. This analysis may be conducted in a selected subset of participants.
COVID-19 cases	Cohort 1 and Cohort 2 combined, Cohort 3: Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized.
Immune response to emerging variants	Cohort 1 and Cohort 2 combined, Cohort 3: For emerging variants (under monitoring, of interest, and/or of concern) not already specified, • GMTs, GMFRs, and percentages of participants with seroresponse at the specific time point, along with the associated 95% CIs, will be summarized in the same way as for the immunogenicity primary endpoints described above. This analysis may be conducted in a selected subset of participants.

Endpoint	Statistical Analysis Methods
Cell-mediated immune response	Cohort 2: The cell-mediated immune response and additional humoral immune response parameters to the SARS-CoV-2 (Omi JN.1) strain will be summarized at each time point for the subset of participants with PBMC samples collected in each group. Cohort 3: The cell-mediated immune response and additional humoral immune response parameters to the SARS-CoV-2 (Omi KP.2) strain will be summarized at each time point for the subset of participants with PBMC samples collected in each group.

10.9.9.4. Interim Analyses

No formal interim analysis will be conducted, as there is no formal hypothesis testing. As this is a sponsor–open-label study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in Section 10.9.9.4.1.

10.9.9.4.1. Analysis Timing

At a minimum, statistical analyses will be carried out when the following data are available, for Cohorts 1 and 2 combined and for Cohort 3:

- Safety and immunogenicity data through Visit C4 (1 month after study vaccination).
- Safety and immunogenicity data through Visit C6 (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.

10.9.9.5. Sample Size Determination

The sample size is not based on any formal hypothesis test. All statistical analyses will be descriptive.

10.10. Appendix 10: Protocol Amendment History

Amendment 1 (11 March 2024)

Overall Rationale for the Amendment:

This amendment adds Substudy C for the evaluation of 1 or 2 BNT162b2-based vaccines, each targeting a predominant circulating variant of SARS-CoV-2. The study will ultimately evaluate the BNT162b2 construct targeting the variant selected for the antigen composition of COVID-19 vaccines to be administered during the 2024-2025 season.

Substudy C will first enroll a smaller group of adults as Cohort 1 to evaluate the safety, tolerability, and immunogenicity of BNT162b2 (Omi JN.1) and possibly a second variant construct (based on epidemiological data) in order to provide early clinical data. A larger group of adolescents and adults will be enrolled into Cohort 2, to evaluate the safety and immunogenicity of the BNT162b2 construct targeting the variant selected for immunization in the 2024-2025 season. It is anticipated that one of the Cohort 1 variants will match the variant selected for the 2024-2025 respiratory season vaccines.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Added ClinicalTrials.gov ID number.	This number was assigned after issue of the original version of the protocol.	Title page
Updated the text to include Substudy C.	To evaluate the BNT162b2 vaccine targeting the SARS-CoV-2 variant selected for the 2024-2025 respiratory virus season.	Section 1 Protocol Summary, Section 1.3 Schedule of Activities, Section 2 Introduction (2.1, 2.2, 2.3), Section 3 Objectives, Endpoints, and Estimands, Section 4.1 Overall Design, Section 9.5.2 Safety Assessment, and Section 10.9 Appendix 9: Substudy C. Additionally, cross-references to the Substudy C appendix sections were added throughout the protocol.
Updated information on the evolution of SARS-CoV-2 variants and the rationale for better-matched COVID-19 vaccines.	To provide background for addition of Substudy C.	Section 1.1 Synopsis, Section 2.1 Study Rationale, Section 2.2 Background.
Updated the clinical overview to add newly published data.	To provide recent data on Substudy A.	Section 2.2.1 Clinical Overview
Updated and condensed information on prior C459 program studies and data.	To provide current information on studies described and to focus the section on more recent clinical data.	Section 2.2.1 Clinical Overview
Made changes to the Substudy C reactogenicity assessment.	To increase/enhance completeness of data, contemporaneous reporting and cohesiveness of CRF reporting.	Section 7.2 Participant Discontinuation/Withdrawal From the Study and Section 8.3.5 Electronic Diary for Reactogenicity: Substudy C.

Description of Change	Brief Rationale	Section # and Name
Clarified that the Substudy C e-diary will not prompt participants to record use of antipyretic/analgesic medications to treat symptoms associated with study vaccination.	With the volume of reactogenicity and antipyretic/analgesic use data that have been collected from previous clinical trials and the number of BNT162b2-based vaccines administered to the public to date, additional data on the use of antipyretic/analgesic medications to treat reactogenicity symptoms are no longer needed.	Section 8.3.5 Electronic Diary for Reactogenicity: Substudy C (does not include references to this).
Nonsubstantial Modification(s)		
Updated the statement regarding the global COVID-19 pandemic.	To reflect that the pandemic has shifted to an endemic.	Section 2.3 Benefit/Risk Assessment.
Revised text around time points for Substudy A and Substudy B N-binding antibody testing to allow flexibility.	The original protocol did not plan for immunogenicity analysis in participants without evidence of infection through each time point. Other than baseline, N-binding antibody testing at later time points is not required for analysis. Updated the text in protocol assessments and SoA sections around N-binding testing time points to align with the plan for immunogenicity analysis. Additionally, Substudy A and Substudy B text now also aligns with Substudy C text in these sections.	Section 10.7.1.3 Schedule of Activities for Substudy A and Section 10.8.1.3 Schedule of Activities for Substudy B; Section 10.7.8.2.3 N-Binding Antibody Test [Substudy A] and Section 10.8.8.2.3 N-Binding Antibody Test [Substudy B].
To the Biological Samples section, added clarification that the details in the second sentence apply to the blinded laboratory analysts.	Laboratory analysts who perform exploratory testing for cell-mediated immunogenicity may not be blinded to the study participant identification number or study visit.	Section 8.2.4 Biological Samples
For Substudy A and Substudy B, added to the e-diary assessments sections that confirmed Grade 4 reactogenicity events are reported in the designated CRF and also in the AE CRF.	To add more details to reflect actual data reporting procedures for Substudy A and Substudy B and to align with the SAP.	Section 8.3.4.2 Local Reactions: Substudy A and Substudy B, Section 8.3.4.3 Systemic Events: Substudy A and Substudy B, and Section 8.3.4.4 Fever: Substudy A and Substudy B.
Clarified that the primary route for SAE reporting is via PSSA and the backup route is using the Vaccine SAE Report Form.	To align with the text in Section 10.3.4.	Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information.
For Substudy C, updated text in the appendix to reflect the current process for contacting an MQI.	The process for contacting an MQI has changed from a medical escalation process via a Pfizer Call Center to direct clinical team contact using a Study Team Contact List.	Section 10.1.12 Sponsor's Medically Qualified Individual.

Description of Change	Brief Rationale	Section # and Name
For Substudy A and Substudy B, added blinding details for laboratory personnel, which were already in place in the study.	No change to the existing blinding plan for laboratory personnel. This was only a correction for inadvertently omitted text in the protocol.	Section 10.7.6.4.3 Blinding of the Sponsor [Substudy A] and Section 10.8.6.4.3 Blinding of the Sponsor [Substudy B].
For Substudy A and Substudy B, added that an unplanned site visit may not occur if the investigator or authorized designee confirms severe reactogenicity assessment via medical records.	This additional reason for why an unplanned visit may not be an on-site visit was in place at the time of original protocol issue but was inadvertently omitted from protocol procedures text.	Section 10.7.8.5.6 Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction [Substudy A] and Section 10.8.8.5.6 Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction [Substudy B].
For Substudy A and Substudy B, added the analysis methods for COVID-19 cases to the statistical analysis methods tables.	No change to the statistical analysis methods. This endpoint was in the original protocol's objectives table. This was only a correction for inadvertently omitted text in the protocol.	Section 10.7.9.3.3 Exploratory Endpoints Analysis [Substudy A] and Section 10.8.9.3.3 Exploratory Endpoints Analysis [Substudy B].
Corrected typographical errors and formatting.	Minor corrections.	Various sections throughout the document.

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
ADL	activities of daily living
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	Pfizer-BioNTech COVID-19 vaccine
CBER	Center for Biologics Evaluation and Research (United States)
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
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	clinical trial
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
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation

Abbreviation	Term
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eICD	electronic informed consent form
EMA	European Medicines Agency
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)
FFRNT	fluorescent focus reduction neutralization test
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
GMR	geometric mean ratio
GMT	geometric mean titer
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
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

Abbreviation	Term
IP	Internet Protocol
IPAL	investigational product accountability log
IPM	investigational product manual
IQR	interquartile range
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
NIMP	noninvestigational medicinal product
Omi	Omicron
OR	odds ratio
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QTL	quality tolerance limit
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

Abbreviation	Term
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SGT	S-gene target
SI	study intervention
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
ULN	upper limit of normal
US	United States
Vax	vaccination
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WT	wild type

11. REFERENCES

1 Liu Y, Liu J, Xia H, et al. BNT162b2-elicited neutralization against new SARS-CoV-2 spike variants [letter]. N Engl J Med. 2021;385(5):472-4.

2 Pfizer. Pfizer and BioNTech receive U.S. FDA emergency use authorization of COVID-19 vaccine booster for individuals 16 years and older [press release]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-receive-us-fda-emergency-use. Published: 09 Dec 2021. Accessed: 02 May 2023.

3 Pfizer. Pfizer and BioNTech announce U.S. FDA approval of their COVID-19 vaccine COMIRNATY® for adolescents 12 through 15 years of age [press release]. Available from: https://www.pfizer.com/news/announcements/pfizer-and-biontech-announce-us-fda-approval-their-covid-19-vaccine-comirnatyr. Published: 08 Jul 2022. Accessed: 08 Feb 2023.

4 Pfizer. Pfizer and BioNTech receive first U.S. FDA emergency use authorization of a COVID-19 vaccine in children ages 5 through 11 years [press release]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-receive-first-us-fda-emergency-use. Published: 29 Oct 2021. Accessed: 02 May 2023.

5 FDA. Pfizer-BioNTech COVID-19 vaccines: Comirnaty, Pfizer-BioNTech COVID-19 vaccine and Pfizer-BioNTech COVID-19 vaccine, bivalent [press release]. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccines. Published: 23 Aug 2021. Accessed: 08 Feb 2023.

6 Pfizer. Pfizer and BioNTech granted FDA emergency use authorization of Omicron BA.4/BA.5-adapted bivalent COVID-19 vaccine booster for ages 12 years and older [press release]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-granted-fda-emergency-use-authorization. Published: 31 Aug 2022. Accessed: 08 Feb 2023.

7 EMA. European public assessment report (EPAR) – Risk management plan. Comirnaty. Available from: https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf. Published: 23 Dec 2020. Updated: 21 Nov 2022. Accessed: 08 Feb 2023.

8 FDA. Coronavirus (COVID-19) update: FDA authorizes changes to simplify use of bivalent mRNA COVID-19 vaccines [press release]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-changes-simplify-use-bivalent-mrna-covid-19-vaccines. Published: 18 Apr 2023. Accessed 29 Jun 2023.

[9] Pfizer and BioNTech. Vaccines and Related Biological Products Advisory Committee Meeting, September 17, 2021. FDA briefing document: BNT162b2 [COMIRNATY (COVID-19 vaccine, mRNA)]: evaluation of a booster dose (third dose). Food and Drug Administration website. Available from: https://www.fda.gov/media/152161/download. Accessed: 12 Jan 2023 and 08 Feb 2023.

[10] Pfizer. Real-world evidence confirms high effectiveness of Pfizer-BioNTech COVID-19 vaccine and profound public health impact of vaccination one year after pandemic declared [press release]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/real-world-evidence-confirms-high-effectiveness-pfizer. Published: 11 Mar 2021. Accessed: 12 Jan 2023 and 08 Feb 2023.

[11] WHO. Weekly epidemiological update on COVID-19 - 11 January 2023. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---11-january-2023. Accessed: 12 Jan 2023.

[12] WHO. Statement on the antigen composition of COVID-19 vaccines. Available from: https://www.who.int/news/item/18-05-2023-statement-on-the-antigen-composition-of-covid-19-vaccines. Published: 18 May 2023. Accessed: 25 May 2023.

[13] CDC. COVID data tracker: variant proportions. Available from: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed: 29 Jul 2024.

[14] Link-Gelles R, Ciesla AA, Roper LE, et al. Early estimates of bivalent mRNA booster dose vaccine effectiveness in preventing symptomatic SARS-CoV-2 infection attributable to Omicron BA.5- and XBB/XBB.1.5-related sublineages among immunocompetent adults - increasing community access to testing program, United States, December 2022-January 2023. MMWR Morb Mortal Wkly Rep 2023;72(5):119-24.

[15] Surie D, DeCuir J, Zhu Y, et al. Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19–associated hospitalization among immunocompetent adults aged ≥65 years — IVY Network, 18 states, September 8–November 30, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(51-52):1625-30.

[16] Tenforde MW, Weber ZA, Natarajan K, et al. Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19–associated emergency department or urgent care encounters and hospitalizations among immunocompetent adults — VISION Network, nine states, September–November 2022. MMWR Morb Mortal Wkly Rep. 2023;71(53):1637-46.

[17] Fabiani M, Mateo-Urdiales A, Sacco C, et al. Protection against severe COVID-19 after second booster dose of adapted bivalent (original/Omicron BA.4-5) mRNA vaccine in persons ≥ 60 years, by time since infection, Italy, 12 September to 11 December 2022. Euro Surveill. 2023;28(8):2300105.

[18] Link-Gelles R, Weber ZA, Reese SE, et al. Estimates of bivalent mRNA vaccine durability in preventing COVID-19–associated hospitalization and critical illness among adults with and without immunocompromising conditions — VISION Network, September 2022–April 2023. MMWR Morb Mortal Wkly Rep. 2023;72(21):579-88.

[19] Poukka E, Nohynek H, Goebeler S, et al. Bivalent booster effectiveness against severe COVID-19 outcomes in Finland, September 2022 — March 2023. medRxiv 2023. DOI: https://doi.org/10.1101/2023.03.02.23286561. Available from: https://www.medrxiv.org/content/10.1101/2023.03.02.23286561v3. Accessed: 30 Jun 2023.

[20] Link-Gelles R. CDC. Data presented at the ACIP meeting (19 April 2023). Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/05-COVID-Link-Gelles-508.pdf. Accessed: 30 Jun 2023.

[21] Lin DY, Xu Y, Gu Y, et al. Effectiveness of bivalent boosters against severe Omicron infection. N Engl J Med. 2023;388(8):764-6.

[22] WHO. Statement on the antigen composition of COVID-19 vaccines. Available from: https://www.who.int/news/item/13-12-2023-statement-on-the-antigen-composition-of-covid-19-vaccines. Published: 13 December 2023. Accessed: 21 Feb 2024.

[23] ECDC, EMA. ECDC-EMA statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants. Available from: https://www.ema.europa.eu/en/documents/other/ecdc-ema-statement-updating-covid-19-vaccines-composition-new-sars-cov-2-virus-variants_en.pdf. Published: 06 Jun 2023. Accessed: 05 Mar 2024.

[24] FDA. Updated COVID-19 vaccines for use in the United States beginning in fall 2023 [press release]. Available from: https://www.fda.gov/vaccines-blood-biologics/updated-covid-19-vaccines-use-united-states-beginning-fall-2023. Published: 16 Jun 2023. Accessed: 05 Mar 2024.

[25] EMA. EMA recommendation to update the antigenic composition of authorized COVID-19 vaccines for 2024-2025. Available from: https://www.ema-recommendation-update-antigenic-composition-authorised-covid-19-vaccines-2024-2025_en.pdf-0 (europa.eu). Published: 30 April 2024. Accessed: 29 July 2024.

[26] WHO. Statement on the antigen composition of COVID-19 vaccines. Available from: https://www.who.int/news/item/26-04-2024-statement-on-the-antigen-composition-of-covid-19-vaccines. Published: 26 Apr 2024. Accessed: 29 July 2024.

[27] EMA. EMA confirms its recommendation to update the antigenic composition of authorized COVID-19 vaccines for 2024-2025. Available from: https://www.ema.europa.eu/en/documents/other/ema-confirms-its-recommendation-update-antigenic-composition-authorised-covid-19-vaccines-2024-2025_en.pdf. Published: 19 July 2024. Accessed: 29 July 2024.

[28] FDA. Updated COVID-19 vaccines for use in the United States beginning in fall 2024. Available from: https://www.fda.gov/vaccines-blood-biologics/updated-covid-19-vaccines-use-united-states-beginning-fall-2024. Published: 13 June 2024. Accessed: 29 July 2024.

[29] Pfizer and BioNTech. Vaccines and Related Biological Products Advisory Committee Meeting Presentation, June 05, 2024. 2024-2025 COVID-19 vaccine formula: Pfizer/BioNTech clinical and preclinical supportive data. FDA website. Available from: https://www.fda.gov/media/179144/download. Accessed: 29 July 2024.

[30] Moderna. Vaccines and Related Biological Products Advisory Committee Meeting Presentation, June 05, 2024. Moderna COVID-19 vaccines update. FDA website. Available from: https://www.fda.gov/media/179142/download. Accessed: 29 July 2024.

[31] Cohen KW, Linderman SL, Moodie Z, et al. Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells. Cell Rep Med. 2021;2(7):100354.

[32] Du L, He Y, Zhou Y, et al. The spike protein of SARS-CoV--a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009;7(3):226-36.

[33] WHO. COVID-19 epidemiological update - 19 January 2024. Available from: https://www.who.int/publications/m/item/covid-19-epidemiological-update---19-january-2024. Accessed: 21 Feb 2024.

[34] WHO. Weekly epidemiological update on COVID-19 - 8 June 2023. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---8-june-2023. Accessed: 01 Mar 2024.

[35] CDC. 2022 Nationwide COVID-19 infection- and vaccination-induced antibody seroprevalence (blood donations). Available from: https://covid.cdc.gov/covid-data-tracker/#nationwide-blood-donor-seroprevalence-2022. Accessed: 12 Feb 2024.

[36] Clarke KEN, Jones JM, Deng Y, et al. Seroprevalence of infection-induced SARS-CoV-2 antibodies — United States, September 2021–February 2022. MMWR Morb Mortal Wkly Rep. 2022;71(17):606-8. DOI: http://dx.doi.org/10.15585/mmwr.mm7117e3.

[37] Link-Gelles R, Ciesla AA, Mak J, et al. Early estimates of updated 2023-2024 (monovalent XBB.1.5) COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection attributable to co-circulating omicron variants among immunocompetent adults - increasing community access to testing program, United States, September 2023-January 2024. MMWR Morb Mortal Wkly Rep. 2024;73(4):77-83. DOI: 10.15585/mmwr.mm7304a2.

[38] Kaku Y, Okumura K, Padilla-Blanco M, et al. Virological characteristics of the SARS-CoV-2 JN.1 variant. Lancet Infect Dis. 2024;24(2):e82.

[39] Yang S, Yu Y, Xu Y, et al. Fast evolution of SARS-CoV-2 BA.2.86 to JN.1 under heavy immune pressure. Lancet Infect Dis. 2024;24(2):e70-2.

[40] Moustsen-Helms IR, Bager P, Larsen TG, et al. Relative vaccine protection, disease severity and symptoms associated with the SARS-CoV-2 Omicron subvariant BA.2.86 and descendant JN.1: a Danish nationwide register-based study. SSRN. Preprint posted: 08 Feb 2024. DOI: 10.2139/ssrn.4716761.

[41] Huiberts AJ, Hoeve CE, de Gier B, et al. Effectiveness of Omicron XBB.1.5 vaccine against SARS-CoV-2 Omicron XBB and JN.1 infection in a prospective cohort study in the Netherlands, October 2023 to January 2024. medRxiv. Preprint posted: 17 Feb 2024. DOI: 10.1101/2024.02.15.24302872.

[42] Carabelli AM, Peacock TP, Thorne LG, et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. Nat Rev Microbiol. 2023, 21:162-77. DOI: https://doi.org/10.1038/s41579-022-00841-7.

[43] Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603-15.

[44] Pfizer and BioNTech. Vaccines and Related Biological Products Advisory Committee Meeting, December 10, 2020. FDA briefing document: Pfizer-BioNTech COVID-19 vaccine. Food and Drug Administration website. Available from: https://www.fda.gov/media/144245/download. Accessed: 13 May 2022.

[45] Pfizer. Pfizer and BioNTech confirm high efficacy and no serious safety concerns through up to six months following second dose in updated topline analysis of landmark COVID-19 vaccine study [press release]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious. Published: 01 Apr 2021. Accessed: 08 Feb 2023.

[46] FDA. Emergency use authorization (EUA) for an unapproved product: review memorandum [Pfizer-BioNTech COVID-19 vaccine BNT162b2 as a single booster dose]. Available from: https://www.fda.gov/media/152432/download. Accessed: 08 Feb 2023.

[47] Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med. 2020;383(25):2439-50.

[48] Pfizer and BioNTech. Safety and efficacy data in support of a planned emergency use authorization amendment for a booster dose of the Pfizer-BioNTech COVID-19 vaccine in individuals 18 years of age and older. EUA 27034. 2021;7:10-2.

[49] Gayed J, Diya O, Lowry FS, et al. Safety and immunogenicity of the monovalent Omicron XBB.1.5-adapted BNT162b2 COVID-19 vaccine in individuals ≥ 12 years old: a phase 2/3 trial. Vaccines. 2024;12(2):118.

[50] Wiemken TL, Khan F, Puzniak L, et al. Seasonal trends in COVID-19 cases, hospitalizations, and mortality in the United States and Europe. Sci Rep. 2023;13(1):3886.

[51] Barouch DH. Covid-19 vaccines – immunity, variants, boosters. N Engl J Med. 2022; 387(11):1011-20.

[52] US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: US Department of Health and Human Services; Sep 2007.

[53] Agresti A. *Introduction: distributions and inference for categorical data*. Chapter 1. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

[54] FDA. Development and licensure of vaccines to prevent COVID-19. Guidance for industry. June 2020. Available from: https://www.fda.gov/media/139638/download. Accessed: 19 Jul 2022.

[55] CDC. People with certain medical conditions. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed: 29 Jun 2023.

[56] CDC. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). Available from: https://www.cdc.gov/mis/mis-c/hcp_cstecdc/index.html. Accessed: 29 Jun 2023.

[57] FDA. September 11, 2023 approval letter COMIRNATY. Available from: https://www.fda.gov/media/172020/download?attachment. Accessed: 04 Mar 2024.

Document Approval Record

Document Name:	C4591054 Protocol Amendment 2, Clean Copy, 07 Aug 2024
Document Title:	A PHASE 2/3 PROTOCOL TO INVESTIGATE THE SAFETY, TOLER ABILITY, AND IMMUNOGENICITY OF BNT162b2 RNA-BASED VAC CINE CANDIDATES FOR SARS-CoV-2 NEW VARIANTS IN HEALTH Y INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	07-Aug-2024 16:02:02	Final Approval
PPD	07-Aug-2024 18:34:15	Final Approval