



**A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF
BNT162b2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH
BNT162b2**

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	BNT162b2 RNA-Based COVID-19 Vaccine
US IND Number:	19736
EudraCT Number:	2021-005197-25
Protocol Number:	C4591031
Phase:	3
Sponsor's Agent's Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

Document History

Document	Version Date
Amendment 12	20 Sep 2023
Amendment 11	20 Sep 2022
Amendment 10	22 Jul 2022
Amendment 9	03 May 2022
Amendment 8	31 Mar 2022
Amendment 7	17 Feb 2022
Amendment 6	08 Feb 2022
Amendment 5	20 Jan 2022
Amendment 4	22 Dec 2021
Amendment 3	28 Oct 2021
Amendment 2	27 Aug 2021
Amendment 1	27 May 2021
Original protocol	13 May 2021

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

Protocol Amendment Summary of Changes Table

Amendment 12 (20 September 2023)

Overall Rationale for the Amendment:

Endpoints and/or analyses that do not pertain to current variant-modified versions of BNT162b2 were removed from Substudy C and Substudy D to expedite the remaining testing and to focus on analyses of interest.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Removed the 6 month time point from the immunogenicity analysis and removed the immune response to VOCs objective for Substudy C	To expedite remaining testing and to focus on analyses of interest	Section 10.9.3 Objectives, Estimands, and Endpoints, Section 10.9.9.3.2 Primary Endpoint(s)/Estimand(s) Analysis, Section 10.9.9.3.4 Exploratory Endpoint(s) Analysis, and Section 10.9.9.4.1 Analysis Timing in Substudy C
Changed the superiority and noninferiority hypotheses G1vG2bA and G2vsG2bA to be descriptive, removed 'super' superiority hypotheses G1vG2bB and G2vG2bB, removed the original objective G5B on noninferiority of anti-Omicron immune response to anti-reference-strain immune response, and renamed G5C to G5B in Substudy D	To expedite remaining testing and to focus on analyses of interest	Section 10.10.3 Objectives, Estimands, and Endpoints, Section 10.10.9.1.2 Statistical Hypothesis, and Section 10.9.9.1.3 Multiplicity Adjustment, Section 10.10.9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis, Section 10.10.9.3.4 Exploratory Endpoint(s) Analysis and Section 10.10.9.4.2 Sample Size Determination in Substudy D
Clarified that the G1vG2bA and G2vsG2bA primary immunogenicity analysis will be performed on evaluable participants with evidence of past SARS-CoV-2 infection in Substudy D	To expedite remaining testing and to focus on analyses of interest	Section 10.10.3 Objectives, Estimands, and Endpoints and Section 10.10.9.3.2 Primary Endpoint(s)/Estimand(s)
Clarified that there is no multiplicity adjustment needed for Cohort 1 in Substudy D	There is no statistical hypothesis in Cohort 1	Section 10.10.9.1.3 Multiplicity Adjustment in Substudy D
Clarified that the statistical hypothesis only applies to Cohort 2 and Cohort 3 in Substudy D	There is no statistical hypothesis in Cohort 1	Section 10.10.9.1.2 Statistical Hypothesis in Substudy D

Description of Change	Brief Rationale	Section # and Name
Updated text in the sample size determination section to state that a random sample of approximately 100 participants with evidence of past SARS-CoV-2 infection from each of Groups 1, 2, and 2b selected from the remaining approximately 175 participants will be used for evaluation of the primary immunogenicity objectives in each group for Cohort 1.	To expedite remaining testing and to focus on analyses of interest	Section 10.10.9.5 Sample Size Determination in Substudy D
Updated the time points of analysis for the exploratory immunogenicity objective from “to describe the immune response to BNT162b2 OMI or BNT162b2 given as the third and/or fourth and/or fifth dose in BNT162b2-experienced participants” to: “For Cohort 1: at baseline, 1 month after the first study vaccination, and 1 month after the second study vaccination (Group 2 only), For Cohort 2: at baseline, 1 month and 3 months after the first study vaccination, 1 month, 3 months, and 6 months after the last study vaccination.”	To expedite remaining testing and to focus on analyses of interest	Section 10.10.3 Objectives, Estimands, and Endpoints and Section 10.10.9.3.4 Exploratory Endpoint(s) Analysis in Substudy D
Updated the time points of analysis for the exploratory immunogenicity objective from “to describe the immune response to BNT162b2 OMI in COVID-19 vaccine-naïve participants” to: “at baseline, 1 month and 6 months after Dose 2, and 1 month and 6 months after Dose 3.”	To expedite remaining testing and to focus on analyses of interest	Section 10.10.3 Objectives, Estimands, and Endpoints in Substudy D

Description of Change	Brief Rationale	Section # and Name
Nonsubstantial Modification(s)		
Added the sponsor's agent's legal address	Added per updated protocol template	Section: Title Page
Added protocol amendment 12 and the version date to the document history table	Added per protocol template requirement	Section: Document History Table
Added overall rationale for protocol amendment 12	Added per protocol template requirement	Section: Protocol Amendment Summary of Changes Table
Added a summary of changes table for protocol amendment 12	Added per protocol template requirement	Section: Protocol Amendment Summary of Changes Table
Moved the overall rationale and summary of changes table for protocol amendment 11 to Appendix 13	Moved per protocol template requirement	Section: Protocol Amendment Summary of Changes Table and Section 10.13 Appendix 13: Protocol Amendment History
Added the rationale for protocol amendment 12 to the introduction for Substudy C and Substudy D	To provide rationale for the amendment	Section 10.9.2.1 Study Rationale for Substudy C and Section 10.10.2.1 Study Rationale for Substudy D

TABLE OF CONTENTS

LIST OF TABLES	19
1. PROTOCOL SUMMARY	20
1.1. Synopsis	20
1.2. Schema	26
1.3. Schedule of Activities	26
2. INTRODUCTION	27
2.1. Study Rationale	27
2.2. Background	28
2.2.1. Clinical Overview	30
2.3. Benefit/Risk Assessment.....	32
2.3.1. Risk Assessment	34
2.3.2. Benefit Assessment.....	36
2.3.3. Overall Benefit/Risk Conclusion.....	36
3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS	36
4. STUDY DESIGN.....	37
4.1. Overall Design.....	37
4.2. Scientific Rationale for Study Design.....	37
4.2.1. Choice of Contraception/Barrier Requirements	37
4.3. Justification for Dose	37
4.4. End of Study Definition	38
5. STUDY POPULATION	38
5.1. Inclusion Criteria.....	38
5.2. Exclusion Criteria.....	38
5.3. Lifestyle Considerations.....	39
5.3.1. Contraception.....	39
5.4. Screen Failures	39
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention	40
6. SPECIFIC STUDY INTERVENTION(S) AND CONCOMITANT THERAPY	40
6.1. Study Intervention(s) Administered	41

6.1.1. Administration	41
6.2. Preparation, Handling, Storage, and Accountability	42
6.2.1. Preparation and Dispensing	43
6.3. Measures to Minimize Bias: Randomization and Blinding.....	43
6.3.1. Allocation to Study Intervention	43
6.3.2. Blinding Arrangements.....	43
6.4. Study Intervention Compliance.....	44
6.5. Dose Modification.....	44
6.6. Continued Access to Study Intervention After the End of the Study.....	44
6.7. Treatment of Overdose.....	44
6.8. Concomitant Therapy	45
6.8.1. Prohibited During the Study	45
6.8.2. Permitted During the Study	46
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL.....	46
7.1. Discontinuation of Study Intervention	46
7.2. Participant Discontinuation/Withdrawal From the Study	47
7.2.1. Withdrawal of Consent	47
7.3. Lost to Follow-Up	48
8. STUDY ASSESSMENTS AND PROCEDURES.....	48
8.1. Efficacy Assessments and/or Immunogenicity Assessments.....	49
8.1.1. Biological Samples	49
8.2. Safety Assessments	50
8.2.1. Physical Examinations.....	50
8.2.2. Vital Signs	50
8.2.3. Clinical Safety Laboratory Assessments	50
8.2.4. Electronic Diary – Applicable Only to Substudies B, C, D, E, and F	50
8.2.4.1. Grading Scales.....	51
8.2.4.2. Local Reactions	51
8.2.4.3. Systemic Events	52
8.2.4.4. Fever.....	53
8.2.4.5. Antipyretic/Analgesic Medication	54

8.2.5. Pregnancy Testing	54
8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting	54
8.3.1. Time Period and Frequency for Collecting AE and SAE Information.....	55
8.3.1.1. Reporting SAEs to Pfizer Safety	57
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF	57
8.3.2. Method of Detecting AEs and SAEs	57
8.3.3. Follow-Up of AEs and SAEs.....	58
8.3.4. Regulatory Reporting Requirements for SAEs.....	58
8.3.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure	58
8.3.5.1. Exposure During Pregnancy.....	59
8.3.5.2. Exposure During Breastfeeding	60
8.3.5.3. Occupational Exposure	61
8.3.6. Cardiovascular and Death Events.....	61
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs.....	61
8.3.7.1. Substudies Including a Potential COVID-19 Illness Visit	61
8.3.7.2. Substudies NOT Including a Potential COVID-19 Illness Visit	62
8.3.8. Adverse Events of Special Interest	62
8.3.8.1. Substudies NOT Including a Potential COVID-19 Illness Visit	62
8.3.8.2. Lack of Efficacy	62
8.3.9. Medical Device Deficiencies.....	62
8.3.10. Medication Errors	63
8.4. Pharmacokinetics	64
8.5. Genetics	64
8.5.1. Specified Genetics	64
8.6. Biomarkers	64
8.7. Immunogenicity Assessments	64
8.8. Health Economics	64
9. STATISTICAL CONSIDERATIONS	64
9.1. Statistical Hypotheses	64

9.1.1. Estimands.....	64
9.1.2. Statistical Hypotheses	64
9.1.3. Multiplicity Adjustments	65
9.2. Analysis Sets	65
9.3. Statistical Analyses	65
9.3.1. General Considerations.....	66
9.3.1.1. Analyses for Binary Data	66
9.3.1.2. Analyses for Continuous Data.....	66
9.4. Interim Analyses	67
9.5. Sample Size Determination	67
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS	68
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations	68
10.1.1. Regulatory and Ethical Considerations	68
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP.....	69
10.1.2. Financial Disclosure	69
10.1.3. Informed Consent Process	69
10.1.4. Data Protection	70
10.1.5. Committees Structure	71
10.1.5.1. Data Monitoring Committee and Other Independent Oversight Committee.....	71
10.1.6. Dissemination of Clinical Study Data	71
10.1.7. Data Quality Assurance	72
10.1.8. Source Documents	74
10.1.9. Study and Site Start and Closure	74
10.1.10. Publication Policy	75
10.1.11. Sponsor’s Qualified Medical Personnel	76
10.2. Appendix 2: Clinical Laboratory Tests	77
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting	78
10.3.1. Definition of AE	78
10.3.2. Definition of an SAE	79

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period.....	80
10.3.4. Reporting of SAEs.....	84
10.4. Appendix 4: Contraceptive and Barrier Guidance	86
10.4.1. Male Participant Reproductive Inclusion Criteria	86
10.4.2. Female Participant Reproductive Inclusion Criteria.....	86
10.4.3. Woman of Childbearing Potential	87
10.4.4. Contraception Methods.....	88
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments	89
10.6. Appendix 6: Alternative Measures During Public Emergencies	91
10.6.1. Telehealth Visits	91
10.7. Appendix 7: Substudy A	92
10.7.1. Substudy Summary	92
10.7.1.1. Synopsis	92
10.7.1.2. Schema	92
10.7.1.3. Schedule of Activities for Substudy A	93
10.7.2. Introduction.....	96
10.7.2.1. Study Rationale	96
10.7.2.2. Background	96
10.7.2.3. Benefit/Risk Assessment.....	96
10.7.3. Objectives, Estimands, and Endpoints.....	96
10.7.4. Study Design.....	98
10.7.4.1. Overall Design.....	98
10.7.4.2. Scientific Rationale for Substudy A Design	98
10.7.4.3. Justification for Dose	99
10.7.4.4. End of Study Definition	99
10.7.5. Study Population.....	99
10.7.5.1. Inclusion Criteria.....	99
10.7.5.2. Exclusion Criteria.....	100
10.7.5.3. Lifestyle Considerations.....	101
10.7.5.4. Screen Failures	102

10.7.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention.....	102
10.7.6. Study Intervention(s) and Concomitant Therapy	102
10.7.6.1. Study Intervention(s) Administered	102
10.7.6.2. Measures to Minimize Bias: Randomization and Blinding	103
10.7.6.3. Study Intervention Compliance.....	104
10.7.6.4. Dose Modification.....	104
10.7.6.5. Continued Access to Study Intervention After the End of the Study	104
10.7.6.6. Treatment of Overdose.....	105
10.7.6.7. Concomitant Therapy	105
10.7.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	105
10.7.8. Study Assessments and Procedures	105
10.7.8.1. Efficacy and/or Immunogenicity Assessments for Substudy A	105
10.7.8.2. Safety Assessments	107
10.7.8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting.....	107
10.7.8.4. Immunogenicity Assessments	107
10.7.8.5. Substudy A Procedures	107
10.7.9. Statistical Considerations for Substudy A	118
10.7.9.1. Statistical Hypotheses	118
10.7.9.2. Analysis Sets	118
10.7.9.3. Statistical Analyses	119
10.7.9.4. Interim Analyses	121
10.7.9.5. Sample Size Determination.....	123
10.8. Appendix 8: Substudy B	125
10.8.1. Substudy Summary.....	125
10.8.1.1. Synopsis	125
10.8.1.2. Schema	125
10.8.1.3. Schedule of Activities for Substudy B	126

10.8.2. Introduction.....	128
10.8.2.1. Study Rationale	128
10.8.2.2. Background	128
10.8.2.3. Benefit/Risk Assessment.....	128
10.8.3. Objectives, Estimands, and Endpoints.....	129
10.8.4. Study Design.....	129
10.8.4.1. Overall Design.....	129
10.8.4.2. Scientific Rationale for Substudy B Design.....	129
10.8.4.3. Justification for Dose	130
10.8.4.4. End of Study Definition	130
10.8.5. Study Population.....	130
10.8.5.1. Inclusion Criteria.....	130
10.8.5.2. Exclusion Criteria.....	131
10.8.5.3. Lifestyle Considerations.....	132
10.8.5.4. Screen Failures	132
10.8.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention.....	132
10.8.6. Study Intervention(s) and Concomitant Therapy	132
10.8.6.1. Study Intervention(s) Administered	133
10.8.6.2. Measures to Minimize Bias: Randomization and Blinding	133
10.8.6.3. Study Intervention Compliance.....	135
10.8.6.4. Dose Modification.....	135
10.8.6.5. Continued Access to Study Intervention After the End of the Study	135
10.8.6.6. Treatment of Overdose.....	135
10.8.6.7. Concomitant Therapy.....	135
10.8.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	135
10.8.8. Study Assessments and Procedures	135
10.8.8.1. Safety Assessments	135
10.8.8.2. Adverse Events, Serious Adverse Events, and Other Safety Reporting.....	135

10.8.8.3. Substudy B Procedures.....	135
10.8.9. Statistical Considerations for Substudy B	143
10.8.9.1. Statistical Hypotheses	143
10.8.9.2. Analysis Sets	144
10.8.9.3. Statistical Analyses	144
10.8.9.4. Interim Analyses	146
10.8.9.5. Sample Size Determination.....	146
10.9. Appendix 9: Substudy C	147
10.9.1. Substudy Summary.....	147
10.9.1.1. Synopsis	147
10.9.1.2. Schema	147
10.9.1.3. Schedule of Activities for Substudy C	148
10.9.2. Introduction.....	150
10.9.2.1. Study Rationale	150
10.9.2.2. Benefit/Risk Assessment.....	151
10.9.3. Objectives, Estimands, and Endpoints.....	151
10.9.4. Study Design.....	152
10.9.4.1. Overall Design.....	152
10.9.4.2. Justification for Dose	153
10.9.4.3. End of Study Definition	153
10.9.5. Study Population.....	153
10.9.5.1. Inclusion Criteria.....	153
10.9.5.2. Exclusion Criteria.....	154
10.9.5.3. Lifestyle Considerations.....	155
10.9.5.4. Screen Failures	155
10.9.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention.....	155
10.9.6. Study Intervention(s) and Concomitant Therapy	156
10.9.6.1. Study Intervention(s) Administered	156
10.9.6.2. Measures to Minimize Bias: Randomization and Blinding	156
10.9.6.3. Study Intervention Compliance.....	158

10.9.6.4. Dose Modification.....	158
10.9.6.5. Continued Access to Study Intervention After the End of the Study.....	158
10.9.6.6. Treatment of Overdose.....	158
10.9.6.7. Concomitant Therapy.....	158
10.9.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal.....	158
10.9.8. Study Assessments and Procedures.....	158
10.9.8.1. Efficacy and/or Immunogenicity Assessments for Substudy C.....	158
10.9.8.2. Safety Assessments.....	158
10.9.8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting.....	158
10.9.8.4. Substudy C Procedures.....	159
10.9.8.5. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis.....	163
10.9.9. Statistical Considerations for Substudy C.....	164
10.9.9.1. Statistical Hypotheses.....	165
10.9.9.2. Analysis Sets.....	165
10.9.9.3. Statistical Analyses.....	165
10.9.9.4. Interim Analyses.....	167
10.9.9.5. Sample Size Determination.....	168
10.10. Appendix 10: Substudy D.....	170
10.10.1. Substudy Summary.....	170
10.10.1.1. Synopsis.....	170
10.10.1.2. Schema.....	171
10.10.1.3. Schedule of Activities for Substudy D.....	174
10.10.2. Introduction.....	187
10.10.2.1. Study Rationale.....	187
10.10.2.2. Benefit/Risk Assessment.....	188
10.10.3. Objectives, Estimands, and Endpoints.....	189
10.10.4. Study Design.....	192
10.10.4.1. Overall Design.....	192

10.10.4.2. Scientific Rationale for Substudy D Design	193
10.10.4.3. Justification for Dose	193
10.10.4.4. End of Study Definition	194
10.10.5. Study Population.....	194
10.10.5.1. Inclusion Criteria.....	194
10.10.5.2. Exclusion Criteria.....	195
10.10.5.3. Lifestyle Considerations.....	196
10.10.5.4. Screen Failures	196
10.10.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention.....	196
10.10.6. Study Intervention(s) and Concomitant Therapy	196
10.10.6.1. Study Intervention(s) Administered	197
10.10.6.2. Measures to Minimize Bias: Randomization and Blinding	197
10.10.6.3. Study Intervention Compliance.....	199
10.10.6.4. Dose Modification.....	199
10.10.6.5. Continued Access to Study Intervention After the End of the Study.....	199
10.10.6.6. Treatment of Overdose	199
10.10.6.7. Concomitant Therapy	199
10.10.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	199
10.10.8. Study Assessments and Procedures	200
10.10.8.1. Surveillance for COVID-19	200
10.10.8.2. Immunogenicity	202
10.10.8.3. Safety Assessments	202
10.10.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting	202
10.10.8.5. Specified Genetics.....	202
10.10.8.6. Substudy D Procedures	202
10.10.9. Statistical Considerations for Substudy D	235
10.10.9.1. Statistical Hypotheses	235
10.10.9.2. Analysis Sets	237

10.10.9.3. Statistical Analyses	237
10.10.9.4. Interim Analyses	240
10.10.9.5. Sample Size Determination	241
10.11. Appendix 11: Substudy E.....	243
10.11.1. Substudy Summary.....	243
10.11.1.1. Substudy Synopsis.....	243
10.11.1.2. Schema	244
10.11.1.3. Schedule of Activities for Substudy E	245
10.11.2. Introduction.....	249
10.11.2.1. Study Rationale	249
10.11.2.2. Benefit/Risk Assessment.....	249
10.11.3. Objectives, Estimands, and Endpoints.....	250
10.11.4. Study Design.....	253
10.11.4.1. Overall Design.....	253
10.11.4.2. Scientific Rationale for Substudy E Design.....	256
10.11.4.3. Justification for Dose	257
10.11.4.4. End of Study Definition	257
10.11.5. Study Population.....	257
10.11.5.1. Inclusion Criteria.....	257
10.11.5.2. Exclusion Criteria.....	258
10.11.5.3. Lifestyle Considerations.....	259
10.11.5.4. Screen Failures	259
10.11.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention.....	259
10.11.6. Study Intervention(s) and Concomitant Therapy	260
10.11.6.1. Study Intervention(s) Administered	260
10.11.6.2. Measures to Minimize Bias: Randomization and Blinding	261
10.11.6.3. Study Intervention Compliance.....	263
10.11.6.4. Dose Modification.....	263
10.11.6.5. Continued Access to Study Intervention After the End of the Study.....	263

10.11.6.6. Treatment of Overdose	263
10.11.6.7. Concomitant Therapy	263
10.11.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	263
10.11.8. Study Assessments and Procedures	263
10.11.8.1. Surveillance for COVID-19	264
10.11.8.2. Immunogenicity	265
10.11.8.3. Safety Assessments	266
10.11.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting	266
10.11.8.5. Specified Genetics	266
10.11.8.6. Substudy E Procedures	266
10.11.9. Statistical Considerations for Substudy E	279
10.11.9.1. Statistical Hypotheses	279
10.11.9.2. Analysis Sets	283
10.11.9.3. Statistical Analyses	283
10.11.9.4. Interim Analyses	286
10.11.9.5. Sample Size Determination	288
10.12. Appendix 12: Substudy F	289
10.12.1. Substudy Summary	289
10.12.1.1. Substudy Synopsis	289
10.12.1.2. Schema	289
10.12.1.3. Schedule of Activities for Substudy F	290
10.12.2. Introduction	292
10.12.2.1. Study Rationale	292
10.12.2.2. Benefit/Risk Assessment	292
10.12.3. Objectives, Estimands, and Endpoints	293
10.12.4. Study Design	293
10.12.4.1. Overall Design	293
10.12.4.2. Scientific Rationale for Substudy F Design	294
10.12.4.3. Justification for Dose	295
10.12.4.4. End of Study Definition	295
10.12.5. Study Population	295

10.12.5.1. Inclusion Criteria.....	295
10.12.5.2. Exclusion Criteria.....	296
10.12.5.3. Lifestyle Considerations.....	297
10.12.5.4. Screen Failures	297
10.12.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention.....	297
10.12.6. Study Intervention(s) and Concomitant Therapy	297
10.12.6.1. Study Intervention(s) Administered	298
10.12.6.2. Measures to Minimize Bias: Randomization and Blinding	299
10.12.6.3. Study Intervention Compliance.....	300
10.12.6.4. Dose Modification.....	300
10.12.6.5. Continued Access to Study Intervention After the End of the Study.....	300
10.12.6.6. Treatment of Overdose	300
10.12.6.7. Concomitant Therapy	300
10.12.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	301
10.12.8. Study Assessments and Procedures	301
10.12.8.1. Surveillance for COVID-19	301
10.12.8.2. Immunogenicity	303
10.12.8.3. Safety Assessments	303
10.12.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting.....	303
10.12.8.5. Substudy F Procedures	303
10.12.9. Statistical Considerations for Substudy F	314
10.12.9.1. Statistical Hypotheses	314
10.12.9.2. Analysis Sets	314
10.12.9.3. Statistical Analyses	314
10.12.9.4. Interim Analyses	316
10.12.9.5. Sample Size Determination.....	317
10.13. Appendix 13: Protocol Amendment History.....	319
10.14. Appendix 14: Abbreviations	356

10.15. Appendix 15: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection	359
10.16. Appendix 16: Genetics	360
11. REFERENCES	361

LIST OF TABLES

Table 1.	Total Number of Participants by Cohort	23
Table 2.	Local Reaction Grading Scale	52
Table 3.	Systemic Event Grading Scale.....	52
Table 4.	Scale for Fever	54
Table 5.	Expected Number of COVID-19 Cases Under Assumed Vaccine Efficacy and Incidence Rate	123
Table 6.	Probability for Vaccine Efficacy Assessment	124
Table 7.	Probability of Observing at Least 1 AE by Assumed True Event Rates	124
Table 8.	Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Samples Sizes.....	146
Table 9.	Probability of Observing at 1 Least AE by Assumed True Event Rates With Different Sample Sizes	169
Table 10.	Total Number of Participants by Cohort	193
Table 11.	Probability of Observing at 1 Least AE by Assumed True Event Rates With Different Sample Sizes	242
Table 12.	Substudy E – Participants >55 Years of Age – Sentinel and Expanded Enrollment	255
Table 13.	Substudy E – Participants 18 to 55 Years of Age – Sentinel and Expanded Enrollment	256
Table 14.	Substudy E – Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes	288
Table 15.	Substudy F – Sentinel and Expanded Enrollment	294
Table 16.	Substudy F - Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes	318

1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title:

A Study to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. In January 2020, the pathogen causing this outbreak was identified as 2019-nCoV. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 11 February 2020, the virus was officially named as SARS-CoV-2, and the WHO officially named the disease caused by SARS-CoV-2 as COVID-19. On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which continues to spread globally at high speed. To-date, more than 455 million people have been infected with SARS-CoV-2 and >6 million have died, demonstrating an urgent need for efficacious vaccines.

Numerous COVID-19 vaccines are currently in development globally, and several candidate COVID-19 vaccines (eg, mRNA vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be efficacious in the prevention of COVID-19 in clinical studies and are now available under temporary or emergency authorizations. BNT162b2, an RNA-based COVID-19 vaccine given as a 2-dose series administered 21 days apart, was shown to be safe and effective in a Phase 1/2/3 study and has received authorizations for temporary or emergency use or marketing authorizations in multiple countries.

Genetic lineages of SARS-CoV-2 have been emerging and circulating around the world since the beginning of the COVID-19 pandemic. There have been at least 12 different variants identified since December 2020. Within the first 3 months of the start of this global pandemic, the Alpha (B.1.1.7 and Q lineages), Beta (B.1.351 and descendent lineages), Gamma (P.1 and descendent lineages), and Epsilon (B.1.427 and B.1.429) variants were identified as VOCs. This is defined as a variant for which there is evidence of an increase in transmissibility, more severe disease, significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatment or vaccines, or diagnostic detection failures. On 21 September 2021, these variants were downgraded to variants being monitored. However, current VOCs include Delta (B.1.617.2 and AY lineages) and Omicron (B.1.1.529 and BA lineages). Delta, which has increased transmissibility, has dominated the number of infections in the latter half of 2021. Since the Omicron variant has been newly identified at the time of this protocol amendment, additional information will be learned as time progresses.

A 2-dose series of BNT162b2 conferred 95% protection against COVID-19 in persons 16 years of age or older after a median follow-up period of 2 months after the second dose. However, as presented in April 2021, the efficacy of BNT162b2 from 7 days through up to 6 months after the second dose had decreased to 91.3% effective against COVID-19.

However, the vaccine was 100% effective against severe disease as defined by the US CDC, and 95.3% effective against severe COVID-19 as defined by the FDA. Recent data from interim analysis of C4591031 Substudy A have demonstrated that a booster dose administered to individuals who previously received a primary 2-dose series of BNT162b2 restored vaccine protection against COVID-19 to the high levels achieved after the second dose, showing a relative VE of 95.6% when compared to those who did not receive the booster. However, the efficacy of BNT162b2 in the face of ongoing emergence of new SARS-CoV-2 variants, with multiple mutations in the S protein, is unknown. Therefore, the substudies within this master protocol will study the safety, and/or immunogenicity, and/or efficacy of various BNT162b2 boosting strategies across different populations of participants (eg, age groups), with the details and rationale for each strategy provided in substudy appendices.

Studying boosting strategies under a single master protocol rather than separate protocols will allow an organized approach that can be easily adapted as data emerge that can impact our understanding of what boosting strategies may be required. This approach will not only be more expeditious to implement, which is critical given the public health emergency the COVID-19 global pandemic represents, but also more readily understandable for investigational sites.

Objectives and Endpoints

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

Estimands

Please refer to the substudy appendices for the rationale of each substudy.

Overall Design

This is a Phase 3 master study to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2. Each substudy design is detailed separately and these substudies may be conducted in parallel, as required by the clinical plan, within the framework of this master protocol.

Substudy A Design

This is a Phase 3 randomized, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥ 16 years of age who have completed a 2-dose primary series of BNT162b2 at least 6 months prior to randomization will be enrolled, and participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomization will be stratified by age, such that approximately 60% of participants enrolled will be ≥ 16 to 55 years of age and approximately 40% of participants > 55 years of age.

Participants who are randomized to receive placebo at the booster vaccination visit will be offered the opportunity to receive BNT162b2 if indicated by the outcome of the interim analyses, or at the discretion of the study sponsor. The timing of this booster vaccination may be informed by the outcome of the interim analyses or at a time decided by the sponsor.

The study may be terminated early, for reasons including (but not limited to) access to and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial. Further to this, participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program will be discontinued from this study.

Substudy B Design

This is a randomized, placebo-controlled, observer-blind, crossover substudy to evaluate the safety and tolerability of a booster (third or fourth) dose of BNT162b2. Participants ≥ 12 years of age to ≤ 30 years of age who have received 2 or 3 doses of BNT162b2 (30- μ g doses) with their last dose at least 4 months (120 days) prior to randomization will be enrolled. Participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo at Visit 1 and the alternative at Visit 3, four weeks later. Randomization will be stratified by age (stratified as 12-17, 18-24, and 25-30 years of age). Approximately 1500 participants will be randomized in the study. A blood sample will be collected to obtain a serum sample for troponin testing before each administration of blinded study intervention, 2 to 5 days after each administration, and 1 month after the second administration.

Substudy C Design

This is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of a booster (third) dose of BNT162b2 at 10 μ g and at 30 μ g. Participants ≥ 12 years of age who have completed a 2-dose primary series of BNT162b2 (30- μ g doses) at least 5 months (150 days) prior to randomization will be enrolled. Participants will be randomized at a ratio of 1:1 to receive BNT162b2 at either a 10- μ g or 30- μ g dose level at Visit 301. Randomization will be stratified by age with escalation to each higher age group guided by immunogenicity results at 7 days after the third dose. A DMC will review safety (e-diary and AE) and immunogenicity data in the first approximately 100 participants with available immunogenicity (~50 participants in each dose level) 7 days after the third dose. Upon confirmation of an acceptable safety and immunogenicity assessment by the DMC, progression of the next age group will occur independently.

As part of Protocol Amendment 11, progression beyond the 12 through 17 years age group will not occur and no further participants will be enrolled. The rationale for this amendment is that a third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time (hence the potential substrate for enrollment is essentially nonexistent) and, for Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine. Both factors contribute to age escalation being operationally unfeasible. Furthermore, since the 30- μ g dose level is well tolerated, and in the

face of emergence of SARS-CoV-2 Omicron sublineages for which a maximum immune response is desirable, the rationale for a reduced dose level no longer holds.

Substudy D Design

This is a randomized substudy composed of open-labeled and observer-blinded groups to evaluate the safety, tolerability, and immunogenicity of a 2-dose primary series of BNT162b2 OMI, and as a booster (third or fourth or fifth) dose at investigator sites in the US and South Africa only. Participants ≥ 18 years of age to ≤ 55 years of age will be enrolled. Approximately 1420 participants will be enrolled in the study.

Participants in Cohort 1 will have completed a 2-dose primary series of BNT162b2 (30- μ g doses), with their last dose 90 to 240 days prior to enrollment. Approximately 615 participants will be randomized at a ratio of 1:1:1 either to receive 1 dose (third) of BNT162b2 OMI, 2 doses (third and fourth) of BNT162b2 OMI, 4 weeks apart, or 1 dose (third) of BNT162b2. Randomization will be stratified by age (stratified as 18-30 and 31-55 years of age). Participants in Cohort 1 will remain blinded to whether they will be receiving a fourth dose through 1 month after their first dose, but the investigator and sponsor will not be blinded.

Participants in Cohort 2 will be enrolled from Study C4591001 and C4591031 Substudy A and will have completed a 2-dose primary series and received a single booster (third) dose of BNT162b2, with their last dose 90 to 180 days prior to randomization. Approximately 600 participants will be randomized at a ratio of 1:1 to receive a fourth dose of either BNT162b2 or BNT162b2 OMI at Visit 401. Participants will be offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up). Randomization will be stratified by age (stratified as 18-30 and 31-55 years of age). Cohort 2 will be observer-blinded.

In Cohort 3, 205 participants 18 through 55 years of age who are COVID-19 vaccine-naïve and have not experienced COVID-19 will be enrolled to receive 2 doses (primary series) of BNT162b2 OMI, 3 weeks apart, with a dose of BNT162b2 approximately 5 months (150 days) later. If participants do not consent to receive BNT162b2 as a third dose, they will not receive a third dose. No participants should receive BNT162b2 OMI as a third dose.

Table 1 details the number of participants by cohort and group, their prior BNT162b2 experience, the vaccine that will be administered, and the number of doses administered as part of Substudy D.

Table 1. Total Number of Participants by Cohort

Cohort	Group	Prior BNT162b2 Experience	Vaccine	Number of Doses Administered as Part of Substudy D	Total Number of Participants
Cohort 1	Group 1	2 Doses	BNT162b2 OMI	1	205
	Group 2	2 Doses	BNT162b2 OMI	2	205
	Group 2b	2 Doses	BNT162b2	1	205

Table 1. Total Number of Participants by Cohort

Cohort	Group	Prior BNT162b2 Experience	Vaccine	Number of Doses Administered as Part of Substudy D	Total Number of Participants
Cohort 2	Group 3	3 Doses	BNT162b2 OMI	1 or 2	300
	Group 4	3 Doses	BNT162b2 (and BNT162b2 OMI at Visit 404)	1 or 2	300
Cohort 3	Group 5	Naïve	BNT162b2 OMI	2	205
			BNT162b2	1	

Note: Cohorts 1 and 2 are observer-blinded. Participants in Cohort 1 will remain blinded to whether they will be receiving a fourth dose through 1 month after their first dose. Cohort 2 participants will be unblinded once they have completed Visit 404. Cohort 3 is open-labeled.

As part of protocol amendment 11, active participants in Cohort 1 and Cohort 2 at the time of this amendment will only be followed for 6 months after their last study vaccination, which aligns with the protocol-specified safety reporting period. As of Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine, and therefore it is unnecessary to prolong the participation of individuals in the study and take immunogenicity samples 12 months after vaccination for the monovalent Omicron vaccine. Their final visit will be V405.

Substudy E Design

This is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 OMI (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), given as a single dose). Approximately 1920 participants >55 years of age and 990 participants 18 to 55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses) with the most recent dose being 5 to 12 months (150 to 360 days) prior to randomization, will be enrolled at investigator sites in the US only. Participants >55 years of age will be randomized at a ratio of 1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 OMI at 30 µg, BNT162b2 OMI at 60 µg, a combination of BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each) at Visit 601 as a fourth dose. Participants 18 to 55 years of age will be randomized to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or BNT162b2 OMI at 60 µg at Visit 601 as a fourth dose.

Initially, for participants >55 years of age, sentinel cohorts (sponsor open-label) of 20 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 30 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 90 sentinel-cohort participants. An IRC will review all reported AEs and reactogenicity e-diary data from the sentinel cohorts collected through Day 7 to allow expanded enrollment of an additional 300 participants per group upon confirmation of

an acceptable safety assessment. If the safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

For participants 18 to 55 years of age, sentinel cohorts (sponsor open-label) of 30 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 15 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 75 sentinel-cohort participants. An IRC will review all reported AEs, reactogenicity e-diary data, and troponin levels from the sentinel cohorts collected through Day 7 to allow expanded enrollment upon confirmation of an acceptable safety assessment. An additional 900 participants will be enrolled and randomized in a 3:1:2 ratio to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg.

Substudy F Design

This is a randomized, observer-blinded substudy to describe the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 OMI (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), given as a single dose. Approximately 180 participants ≥60 years of age who have received 3 prior doses of BNT162b2 (30 µg doses), with the most recent dose being ≥4 months prior to randomization, will be enrolled in Israel. Participants will be randomized at a ratio of 1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 OMI at 30 µg, BNT162b2 OMI at 60 µg, a combination of BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each) at Visit 701 as a fourth dose.

Initially, sentinel cohorts (sponsor open-label) of 5 participants per group will be enrolled. An IRC and site representatives will review all reported AEs and reactogenicity e-diary data from the sentinel cohorts collected through Day 7 to allow expanded enrollment of an additional 25 participants per group upon confirmation of an acceptable safety assessment. If the safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

Number of Participants

Substudy A will include 10,000 participants.

Substudy B will include up to 1500 participants.

Substudy C will include up to 150 participants.

Substudy D will include up to 1420 participants.

Substudy E will include up to 2910 participants.

Substudy F will include up to 180 participants.

Data Monitoring Committee or Other Independent Oversight Committee

An external DMC will be formed and will review cumulative unblinded data throughout the study.

Substudy C will utilize a DMC that will be used to review safety and immunogenicity data in the first approximately 100 participants with available immunogenicity data (~50 participants in each dose level of BNT162b2) 7 days after the third dose.

Substudies E and F will utilize an IRC that will be used to review all reported AEs and reactogenicity data collected through Day 7 from all participants enrolled in the sentinel cohorts to evaluate if enrollment can be expanded in each group.

Statistical Methods:

The statistical methods will be specified in the respective substudy appendices.

1.2. Schema

Please refer to the 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.

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.

Refer to the SoA for Substudy A in [Section 10.7.1.3](#), for Substudy B in [Section 10.8.1.3](#), for Substudy C in [Section 10.9.1.3](#), Substudy D in [Section 10.10.1.3](#), Substudy E in [Section 10.11.1.3](#) and Substudy F in [Section 10.12.1.3](#).

2. INTRODUCTION

BNT162b2 is an RNA-based COVID-19 vaccine that is currently being investigated for the prevention of COVID-19 in individuals ≥ 6 months of age. On 02 December 2020, the MHRA in the UK granted a temporary authorization.¹ On 11 December 2020, the US FDA issued an EUA for use in individuals 16 years of age and older. BNT162b2 has now been granted a conditional marketing authorization, EUA, or temporary authorization in a total of more than 60 countries^{2,3,4} and has been fully licensed for use in individuals 16 years of age and above in the US as of 23 August 2021.⁵

2.1. Study Rationale

Like other COVID-19 vaccines recently developed, the long-term persistence of immunity and efficacy of BNT162b2 has yet to be studied. In addition, genetic lineages of SARS-CoV-2 have been emerging and circulating around the world since the beginning of the COVID-19 pandemic. There have been at least 12 different variants identified since December 2020. Within the first 3 months of the start of this global pandemic, the Alpha (B.1.1.7 and Q lineages), Beta (B.1.351 and descendent lineages), Gamma (P.1 and descendent lineages), and Epsilon (B.1.427 and B.1.429) variants were identified as VOCs. This is defined as a variant for which there is evidence of an increase in transmissibility, more severe disease, significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatment or vaccines, or diagnostic detection failures. On 21 September 2021, these variants were downgraded to variants being monitored. However, current VOCs include Delta (B.1.617.2 and AY lineages) and Omicron (B.1.1.529 and BA lineages). Delta, which has increased transmissibility, has dominated the number of infections in the latter half of 2021. Since the Omicron variant has been newly identified at the time of this protocol amendment, additional information will be learned as time progresses.⁶

A 2-dose series of BNT162b2 conferred 95% protection against COVID-19 in persons 16 years of age or older after a median follow-up period of 2 months after the second dose.⁷ However, as presented in April 2021, the efficacy of BNT162b2 from 7 days through up to 6 months after the second dose had decreased to 91.3% effective against COVID-19. However, the vaccine was 100% effective against severe disease as defined by the US CDC, and 95.3% effective against severe COVID-19 as defined by the FDA.⁸ Recent data from interim analysis of C4591031 Substudy A have demonstrated that a booster dose administered to individuals who previously received a primary 2-dose series of BNT162b2 restored vaccine protection against COVID-19 to the high levels achieved after the second dose, showing a relative VE of 95.6% when compared to those who did not receive the booster.⁹ However, the efficacy of BNT162b2 in the face of recurring emergence of new SARS-CoV-2 variants, with multiple mutations in the S protein, is unknown. Therefore, the substudies within this master protocol will evaluate the safety, and/or immunogenicity, and/or efficacy of various BNT162b2 boosting strategies across different populations of participants (eg, age groups) having previously received 2 doses of BNT162b2 administered 21 days apart, with the details and rationale for each strategy provided in the substudy appendices ([Section 10.7](#) through [Section 10.12](#)).

Studying boosting strategies under a single master protocol, rather than separate protocols, will allow an organized approach that can be easily adapted as data emerge that can impact our understanding of what boosting strategies may be required. This approach will not only be more expeditious to implement, which is critical given the public health emergency the COVID-19 global pandemic represents, but also more readily understandable for investigational sites.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that 2019-nCoV was the underlying cause. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020.¹⁰ On 11 February 2020, the virus was officially named as SARS-CoV-2, and the WHO officially named the disease caused by SARS-CoV-2 as COVID-19.^{10,11} SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, and on 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.¹² To-date, more than 455 million people have been infected with SARS-CoV-2 and >6 million have died, demonstrating an urgent need for efficacious vaccines.¹³

Numerous COVID-19 vaccines are currently in development globally, and several candidate COVID-19 vaccines (eg, mRNA vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be efficacious in the prevention of COVID-19 in clinical studies and are now available under temporary or emergency authorizations.¹⁴ BNT162b2, an RNA-based COVID-19 vaccine given as a 2-dose series administered 21 days apart, was shown to be safe and effective in a Phase 1/2/3 study and has received authorizations for temporary or emergency use or marketing authorizations in multiple countries and has been fully licensed for use in individuals 16 years of age and above in the US as of 23 August 2021.^{5,15}

Recent evolution of SARS-CoV-2 is resulting in an emergence of new virus variants with multiple mutations in the S protein, which might be associated with the lower efficacy of some of the current vaccines. Therefore, there is a need to continue research including new approaches, such as evaluation of booster doses, to overcome waning immunity and/or the development of modified vaccines.¹⁶

Substudy B

Myocarditis and pericarditis are inflammatory conditions of the myocardium and the pericardium, respectively. A definitive diagnosis of myocarditis requires histological or immunohistological confirmation of an endomyocardial biopsy or other tissue specimen (eg, from an autopsy). Because of their invasive nature, biopsies are rarely obtained, and therefore a diagnosis of myocarditis is often based upon a compatible clinical scenario associated with noninvasive biomarker and imaging features.¹⁷ This results in case definitions that are very complex, potentially based on multiple parameters (eg, Brighton Collaboration definitions).¹⁸

Abnormal ECG, echocardiogram, or troponin findings consistent with myocarditis with no cardiac symptoms have been reported in association with SARS-CoV-2 infection¹⁹ but are not well characterized phenomena, and there is no widely accepted definition of subclinical myocarditis.

Substudy C

The results from 306 18- to 55-year-old participants from the C4591001 study who received a third (booster) dose of BNT162b2 30 µg a median of 6.8 months after their second dose demonstrated a strong immune response. The geometric mean neutralizing antibody titers against the reference strain were more than 3 times higher 1 month after the booster dose compared to 1 month after Dose 2.²⁰ Immunogenicity of the primary series in participants 12 to 15 of age was shown to be greater than in participants 16 to 25 years of age.²¹ Further, a lower dose may produce a more favorable reactogenicity profile, with the additional benefit that it could improve vaccine accessibility by making more doses available. Therefore, the assessment of a 10-µg booster dose in individuals ≥12 years of age who have received the authorized 30-µg 2-dose primary series warrants further investigation.

Substudy D

On 24 November 2021, South Africa reported the identification of a new SARS-CoV-2 variant, B.1.1.529, to the WHO; the new variant has been named Omicron and has now been detected globally. The Omicron variant has many concerning spike protein mutations, some of which are known from other variants to be associated with reduced neutralization by convalescent and vaccinee sera. In regard to transmissibility, it is currently clear that Omicron spreads more efficiently from person to person.²² However, it is unclear if infection with Omicron is associated with more severe disease.²³ Lastly, preliminary data announced on 08 December 2021 from an initial laboratory study demonstrated that serum antibodies induced by BNT162b2 neutralize the SARS-CoV-2 Omicron variant after 3 doses. Sera obtained from vaccinees 1 month after receiving the booster vaccination (third dose of BNT162b2) neutralized the Omicron variant to levels that are comparable to those observed for the wild-type SARS-CoV-2 spike protein after 2 doses. A third dose also strongly increases CD8⁺ T-cell levels against multiple spike protein epitopes, which are considered to correlate with the protection against severe disease. Compared to the wild-type virus, the vast majority of these epitopes remain unchanged in the Omicron spike variant.²⁴ Therefore, Substudy D has been designed to assess an Omicron-specific vaccine clinically.

Substudies E and F

The SARS-CoV-2 variant B.1.1.529, also known as Omicron, was identified on 24 November 2021. As of 08 January 2022, it is now the dominant variant within the US, identified in 98.3% of sequenced COVID-19 cases.²⁵ It is currently unknown whether a single booster dose of BNT162b2, which has previously been demonstrated to have 95% clinical efficacy against SARS-CoV-2 (Delta being the dominant variant), will be as effective against the Omicron variant.

Data published on 31 December 2021 from the UK consisted of 2 studies examining the association between both variant and vaccination status and risk of hospitalization. Study 1 assessed the risk of hospitalization, and Study 2 assessed vaccine effectiveness against symptomatic infection and hospitalization. The results for Study 1 noted that the risk of hospitalization was lower for Omicron cases after 2 and 3 doses of vaccine, with an 81% (77%-85%) reduction in the risk of hospitalization after 3 doses compared to unvaccinated Omicron cases. With regard to Study 2, the vaccine effectiveness against hospitalization was 88% (78%-93%) for Omicron cases after 3 doses of vaccine.²⁶

A recent laboratory study compared the neutralization of Omicron-infected cells in serum samples obtained from participants who had received 2 doses of BNT162b2 with neutralization in samples obtained from participants who had received 3 doses of BNT162b2. The neutralization efficiency of the BNT162b2 vaccine was also tested against wild-type SARS-CoV-2 and the Beta, Delta, and Omicron variants. The importance of a third vaccine dose was evidenced by a higher neutralization efficiency (by a factor of 100) against the Omicron variant after the third dose than after the second dose. However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant.²⁷ Therefore, the addition of a higher-dose booster may improve protection, particularly in older individuals, with increased longevity of an immune response, provided it has a tolerable safety profile. Therefore, Substudies E and F have been designed to evaluate high-dose BNT162b2 OMI (60 µg), high-dose BNT162b2 (60 µg), and a high-dose combination of BNT162b2 OMI and BNT162b2 (30 µg of each), compared to BNT162b2 OMI 30 µg, BNT162b2 30 µg, and a combination of BNT162b2 OMI and BNT162b2 (15 µg of each), given as a fourth dose.

2.2.1. Clinical Overview

Study C4591001 (NCT04368728) is an ongoing Phase 1/2/3 trial in ~46,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from a novel RNA-based vaccine candidate.⁷ The trial is being conducted in a heterogeneous study population: eligible participants ≥12 years of age, healthy participants, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants. The study consists of 2 parts: Phase 1: to identify the preferred vaccine candidate (BNT162b1 or BNT162b2) and dose level (10 µg, 20 µg, 30 µg, or 100 µg [for BNT162b1]); Phase 2/3: an expanded-cohort and efficacy part for the selected vaccine candidate (BNT162b2).

The available immunogenicity data from Phase 1 participants show that BNT162b2 induced a robust IgG-binding response to S1 and a SARS-CoV-2–neutralizing response. Immunogenicity substantially increased following the second dose of vaccine. BNT162b2 induces a strong antigen-specific Th1-skewed CD4+ response and a strong antigen-specific CD8+ response. BNT162b2 was selected from the Phase 1 part of the study based on the overall safety, tolerability, and immunogenicity. In a mid-November 2020 analysis of 36,621 participants randomized 1:1 to vaccine or placebo, who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination schedule, the efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine

was 95.0%, with 8 COVID-19 cases in the active vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, sexes, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.²⁸

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 to 6 months after the second dose.²⁹ Furthermore, from the same analysis, BNT162b2 was shown to have an efficacy of:

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

Safety data from approximately 38,000 participants at least 16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose demonstrated a favorable safety profile. Available safety data from all participants enrolled through the 14 November 2020 data cutoff (N=43,252, which includes late enrollment of additional adolescent and adult participants) were consistent with the safety profile for the approximately 38,000 participants with a median follow-up of 2 months and also did not raise specific safety concerns.²⁸

The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), and fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants ≥ 55 years of age ($\leq 2.8\%$) as compared to younger participants ($\leq 4.6\%$). The frequency of SAEs was low ($<0.5\%$), without meaningful imbalances between study arms. Lymphadenopathy was observed in 0.3% of vaccine recipients as compared to $<0.1\%$ of those who received placebo. Otherwise, there were no notable patterns or numerical imbalances between vaccine groups for specific categories of nonserious AEs (including other neurologic, neuroinflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2. With the exception of more frequent, generally mild to moderate reactogenicity in participants <55 years of age, the safety profile of BNT162b2 was generally similar across age groups, sexes, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.²⁸

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-19.³⁰ On 19 November 2021, the FDA amended the EUA, authorizing use of a single booster dose for all individuals 18 years of age and older after completion of primary vaccination with an FDA-approved COVID-19 vaccine.³¹ On 09 December 2021, the FDA again amended the EUA to authorize the use of a single booster dose for administration to individuals 16 and 17 years of age at least 6 months after completion of primary vaccination with BNT162b2.³² In addition, a booster dose of the vaccine is authorized in the EU and other countries, with recommendations for populations varying based on local health authority guidance.^{33,34}

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

Symptomatic COVID-19 occurrence was measured from ≥ 7 days after booster or placebo, with a median follow-up of 2.5 months. During the blinded placebo-controlled study period up to a data cutoff date of 05 October 2021, there were a total of 6 cases of COVID-19 in the booster group, and 123 cases in the nonboosted placebo group, in the evaluable efficacy population without evidence of prior SARS-CoV-2 infection. The observed relative VE was 95.3% (2-sided 95% CI: 89.5%, 98.3%), which reflects the reduction in disease occurrence in the boosted group versus the nonboosted group. The AE profile was generally consistent with other previously submitted clinical safety data for the vaccine, with no new safety concerns identified. No cases of myocarditis or pericarditis were reported.³⁵

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no approved or licensed preventive or therapeutic options available. However, based on the data available from the C4591001 study, multiple temporary or EUAs have been granted. The available safety and immunogenicity data from the ongoing Pfizer-BioNTech clinical trial combined with available nonclinical data with BNT162 vaccines and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, support a favorable benefit/risk profile and support continued clinical development of BNT162b2.

In the C4591001 study, BNT162b2 has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), and fever (14.2%).²⁸ Adverse reactions characterized as reactogenicity were generally mild to moderate. The number of participants reporting hypersensitivity-related AEs was numerically higher in the vaccine group compared with the placebo group (137 [0.63%] vs 111 [0.51%]). Severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in older adults (>55 years of age) ($\leq 2.8\%$) as compared to younger participants ($\leq 4.6\%$). Among reported unsolicited AEs, lymphadenopathy occurred much more frequently in the active vaccine group than the placebo group and is plausibly related to vaccination. SAEs, while uncommon ($< 1.0\%$), represented medical events that occur in the general population at similar frequency as observed in the study.²⁸

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. The risks are based on the observed safety profile to date, which shows mostly mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations. The preponderance of severe cases of COVID-19 in the placebo group relative to the BNT162b2 group (9 of 10) suggests no evidence of VAED.²⁸

In the latest analysis from C4591001, vaccine safety has been evaluated in more than 44,000 participants ≥ 16 years of age, with more than 12,000 vaccinated participants having at least 6 months follow-up after their second dose. No serious safety concerns have been observed in this timeframe. Side effects observed in this analysis were generally consistent with previously reported results.²⁹

Continued clinical investigation is justified, given:

- the threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection.
- the potential of the BioNTech platform of RNA-based vaccines to deliver high numbers of vaccine doses rapidly in a single production campaign.
- the threat posed by the SARS-CoV-2 variants emerging worldwide.
- the potential need for enhancing immunoresponses to overcome waning immunity.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162b2 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): BNT162b2 RNA-Based COVID-19 Vaccine		
Local reactions and systemic events may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines as well as the COVID-19 vaccine. The most common events reported in Study C4591001 were mild to moderate pain at the injection site, fatigue, and headache. ²⁸	<ul style="list-style-type: none"> Local reactions and systemic events will be recorded as AEs or captured in an e-diary (in Substudies B, C, D, E, and F). All study participants will be observed for at least 30 minutes after vaccination. Given that higher dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI will be administered in Substudies E and F, these substudies will include review of e-diary data reported through Day 7 from sentinel cohorts of 20 participants per group in Substudy E and 5 participants per group in Substudy F by an IRC before expanding enrollment. See Sections 10.11.4.1 and 10.12.4.1 for details.
<p>Safety profile of a novel vaccine not yet fully characterized.</p> <p>Adverse reactions (risks) identified from the postauthorization safety data include the following: anaphylaxis, other hypersensitivity reactions (eg, rash, pruritus, urticaria, angioedema), pain in extremity (injected arm), vomiting, and diarrhea.</p>	<p>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.²⁸</p> <p>Postauthorization safety data surveillance has confirmed the safety profile observed in C4591001 and has resulted in identification of some additional adverse reactions (risks) as noted in this table.</p>	<ul style="list-style-type: none"> Collection of AEs from signing of the ICD through 1 month after the booster or last study vaccination. Collection of SAEs from signing of the ICD through 6 months after the booster or last study vaccination. DMC review throughout the study to review all safety data. All participants will be observed for at least 30 minutes after vaccination. Given that higher dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI will be administered in Substudies E and F, these substudies will include review of AE data reported through Day 7 from sentinel cohorts of 20 participants per group in Substudy E and 5 participants

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		per group in Substudy F by an IRC before expanding enrollment. See Sections 10.11.4.1 and 10.12.4.1 for details.
Theoretical risk for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with RSV, feline coronavirus, and Dengue virus vaccines. It is a modified and/or severe presentation of an infectious disease affecting individuals exposed to the wild-type pathogen after having received vaccine designed to prevent infection. No evidence of disease enhancement has been seen in large-scale clinical study of BNT162b2 in humans or in postauthorization surveillance.	Monitoring for cases of COVID-19 developing during the study, which will be reported at COVID-19 illness visits for substudies that include those visits or as AESIs for those substudies that do not. Assessments of individual cases for disease enhancement is challenging based on current understanding of mechanism of pathogenesis, thus evaluations of any adverse or unexpected imbalances in severe COVID-19 cases may provide insight to a potential signal for this theoretical risk.
Very rare cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.	Anaphylaxis: The estimated rate is 5.0 per million doses administered. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases, 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.	Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 10.7.8.5.9 for Substudy A, Section 10.8.8.3.6 for Substudy B, Section 10.9.8.5 for Substudy C, Section 10.10.8.6.7 for Substudy D, Section 10.11.8.6.12 for Substudy E, and Section 10.12.8.5.10 for Substudy F.

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	<ul style="list-style-type: none"> Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Monitoring for cases of COVID-19 developing during the study, which will be reported as AESIs.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants enrolled in Substudy A are detailed in [Section 10.7.2.3.1](#), for Substudy B in [Section 10.8.2.3.1](#), for Substudy C in [Section 10.9.2.2.1](#), Substudy D in [Section 10.10.2.2.1](#), for Substudy E in [Section 10.11.2.2.1](#), and for Substudy F in [Section 10.12.2.2.1](#).

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risks to participants participating in each substudy, the potential risks identified in association with BNT162b2 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](#).

For Substudy C, refer to [Section 10.9.3](#).

For Substudy D, refer to [Section 10.10.3](#).

For Substudy E, refer to [Section 10.11.3](#).

For Substudy F, refer to [Section 10.12.3](#).

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3 master study to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2. Each substudy design is detailed in [Section 10.7](#) through [Section 10.12](#). Each substudy may be conducted in parallel, as required by the clinical plan, within the framework of this master protocol.

4.2. Scientific Rationale for Study Design

Refer to [Section 2.1](#) for the master protocol study rationale.

See the substudy appendices for the rationales supporting each substudy.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for BNT162b2, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see [Appendix 4](#)) if indicated by the substudy eligibility criteria.

4.3. Justification for Dose

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

The vaccine candidate BNT162b1 was initially studied in clinical trial C4591001, but BNT162b2 was selected for Phase 2/3 development due to its better tolerability profile.³⁶ While the 30-µg dose level of BNT162b2 was advanced, higher dose levels of BNT162b1 (50 µg, 60 µg, and 100 µg) were studied in 18- to 55-year-old participants.^{37,38} Due to the level of reactogenicity observed, these dose levels were not advanced. The Phase 2/3 part of clinical trial C4591001 demonstrated that systemic reactogenicity was higher in 16- to 55-year-olds compared to those older than 55 years of age.⁷ In light of better tolerability in older adults, the waning of efficacy observed, and the immune escape exhibited by the Omicron variant, study of a higher dose of the vaccine is warranted.

For Substudies E and F, high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2, given as a fourth dose, will be evaluated. BNT162b2 at a dose of 30 µg will be used as a control in Substudies E and F.

4.4. End of Study Definition

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

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreener for study recruitment purposes 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 substudy-specific inclusion criteria are met.

For Substudy A, see [Section 10.7.5.1](#).

For Substudy B, see [Section 10.8.5.1](#).

For Substudy C, see [Section 10.9.5.1](#).

For Substudy D, see [Section 10.10.5.1](#).

For Substudy E, see [Section 10.11.5.1](#).

For Substudy F, see [Section 10.12.5.1](#).

Some inclusion criteria are common to all substudies: participants (and their parent[s]/legal guardian[s]) willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures; participants should be healthy; and participants (or their parent[s]/legal guardian[s]) must be capable of giving personal signed informed consent.

5.2. Exclusion Criteria

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

Some exclusion criteria are common to all substudies: participants with medical or psychiatric conditions that may increase the risk of study participation; history of severe adverse reactions associated with a vaccine and/or severe allergic reaction to any component of the study vaccination; previous clinical or microbiological diagnosis of COVID-19; immunocompromised individuals; or participants with bleeding diathesis.

For Substudy A, see [Section 10.7.5.2](#).

For Substudy B, see [Section 10.8.5.2](#).

For Substudy C, see [Section 10.9.5.2](#).

For Substudy D, see [Section 10.10.5.2](#).

For Substudy E, see [Section 10.11.5.2](#).

For Substudy F, see [Section 10.12.5.2](#).

5.3. Lifestyle Considerations

5.3.1. Contraception

The following section is applicable if indicated by the substudy eligibility criteria.

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her 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. At time points indicated in the [SoA](#), the investigator or designee will inform the participant of the need to use highly 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 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 assigned to study intervention. 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, eligibility criteria, and any SAEs.

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

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

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met. Participants meeting these criteria at Vaccination 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

- Current febrile illness (body temperature $\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
 - 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.
- Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
- Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
- Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. SPECIFIC STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

For the purposes of the master protocol, study intervention refers to the 30 µg dose level of BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S). Additional study intervention(s) are detailed for each substudy, if applicable. Additional study interventions administered in Substudy A are detailed in [Section 10.7.6](#), Substudy B in [Section 10.8.6](#), Substudy C in [Section 10.9.6](#), Substudy D in [Section 10.10.6](#), Substudy E in [Section 10.11.6](#), and Substudy F in [Section 10.12.6](#).

Intervention Name	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)
Type	Vaccine
Dose Formulation	modRNA
Unit Dose Strength(s)	250 µg/0.5 mL
Dosage Level(s)	30-µg
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement

6.1.1. Administration

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

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

Study intervention administration details will be recorded on the CRF.

See [Section 10.7.6.1.1](#) for further study intervention administration details for Substudy A.

See [Section 10.8.6.1.1](#) for further study intervention administration details for Substudy B.

See [Section 10.9.6.1.1](#) for further study intervention administration details for Substudy C.

See [Section 10.10.6.1.1](#) for further study intervention administration details for Substudy D.

See [Section 10.11.6.1.1](#) for further study intervention administration details for Substudy E.

See [Section 10.12.6.1.1](#) for further study intervention administration details for Substudy F.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions 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 or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.
3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, 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 definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.
4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.
5. Study interventions should be stored in their original containers.
6. See the IP manual for storage conditions of the study intervention once diluted.
7. The investigator, institution, or the head of the medical institution (where applicable) 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 IP manual. 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 IP manual.

6.2.1. Preparation and Dispensing

See the IP manual 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 preparation and dispensing.

See [Section 10.7.6.1.2](#) for additional preparation and dispensing details for Substudy A.

See [Section 10.8.6.1.2](#) for additional preparation and dispensing details for Substudy B.

See [Section 10.9.6.1.2](#) for additional preparation and dispensing details for Substudy C.

See [Section 10.10.6.1.2](#) for additional preparation and dispensing details for Substudy D.

See [Section 10.11.6.1.2](#) for additional preparation and dispensing details for Substudy E.

See [Section 10.12.6.1.2](#) for additional preparation and dispensing details for Substudy F.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

Study intervention will be dispensed at the study visits summarized in the [SoA](#).

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

6.3.2. Blinding Arrangements

Blinding arrangements for site personnel and the sponsor for Substudy A are detailed in [Section 10.7.6.2.1](#) and [Section 10.7.6.2.2](#).

Blinding arrangements for site personnel and the sponsor for Substudy B are detailed in [Section 10.8.6.2.1](#) and [Section 10.8.6.2.2](#).

Blinding arrangements for site personnel and the sponsor for Substudy C are detailed in [Section 10.9.6.2.1](#) and [Section 10.9.6.2.2](#).

Blinding arrangements for site personnel and the sponsor for Substudy D are detailed in [Section 10.10.6.2.1](#) and [Section 10.10.6.2.2](#).

Blinding arrangements for site personnel and the sponsor for Substudy E are detailed in [Section 10.11.6.2.1](#) and [Section 10.11.6.2.2](#).

Blinding arrangements for site personnel and the sponsor for Substudy F are detailed in [Section 10.12.6.2.1](#) and [Section 10.12.6.2.2](#).

6.4. Study Intervention Compliance

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

6.5. Dose Modification

Not applicable.

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

For Substudies A, B, D, E, and F, no intervention will be provided to study participants at the end of their study participation.

For Substudy C, if the 10-µg dose is found to have a suboptimal immune response, as determined by the sponsor, this group will be offered a single 30-µg dose.

6.7. 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 medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
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**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

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

- Any vaccinations received from 28 days prior to study enrollment until 28 days following administration of the last study intervention.
- Prohibited medications listed in Section 6.8.1 will be recorded to include start and stop dates, name of the medication, dose, unit, route, and frequency.

6.8.1. 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 and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (unless documented as per [Section 7](#)). Medications should not be withheld if required for a participant's medical care.

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine 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, or radiotherapy, within 60 days before enrollment through conclusion of the study.
- Receipt of systemic corticosteroids (≥ 20 mg/day of prednisone or equivalent) for ≥ 14 days is prohibited from 28 days prior to enrollment through 28 days after administration of the last study intervention.
- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19 within 90 days before enrollment through conclusion of the study.
- Receipt of any other (nonstudy) coronavirus vaccine at any time during study participation is prohibited.
- Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.8.2. Permitted During the Study

Medication other than that described as prohibited in [Section 6.8.1](#) required for treatment of preexisting conditions or acute illness is permitted.

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

Hormonal contraceptives that meet the requirements of this study can be used in participants who are WOCBP (see [Appendix 4](#)).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

*A positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. If study intervention (other than Dose 1) has been delayed per [Section 5.5](#), because of febrile or other acute illness (Item 1 in the [Section 5.5](#) list), and the investigator later diagnoses the signs and symptoms as COVID-19 (with or without a positive SARS-CoV-2 NAAT result), the participant may receive a further dose of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and immunogenicity. See the [SoA](#) for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed. Participants who remain in the study for evaluation of safety will be contacted by telephone 6 months after their last study vaccination to record AEs as described in [Section 8.3](#).

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant or parent/legal guardian request;
- Investigator request;
- Protocol deviation (Note: from site receipt of a PACL dated 21 September 2021, receipt of a nonstudy COVID-19 vaccine during study participation will result in study withdrawal).

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

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

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

7.2.1. Withdrawal of Consent

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

should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, he or she may request to know which study intervention he or she received at Visit 1 without needing to reconsent.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she 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 attend 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, he/she 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, [Section 10.8.8](#) for Substudy B, [Section 10.9.8](#) for Substudy C, [Section 10.10.8](#) for Substudy D, [Section 10.11.8](#) for Substudy E, and [Section 10.12.8](#) for Substudy F.

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

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

Study procedures and their timing are summarized in the [SoA](#). Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

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 may 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 he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

8.1. Efficacy Assessments and/or Immunogenicity Assessments

Serum samples may be obtained for immunogenicity testing at the visits specified in the substudy [SoA](#) and assays performed as detailed for each substudy.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer (and by the site [Sheba] and BioNTech for Substudy F). Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other vaccines or vaccine-related products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

The participant may request that his or her 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 genetic material is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

8.2. Safety Assessments

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

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

AEs and SAEs are collected, recorded, and reported as defined in [Section 8.3](#).

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

For Substudies B, C, D, E, and F:

The safety parameters also include reactogenicity e-diary reports of local reactions, systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in [Section 8.2.4](#).

8.2.1. Physical Examinations

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

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 8.3.1](#) to [Section 8.3.3](#).

8.2.2. Vital Signs

The participant's body temperature will be measured prior to each vaccination.

8.2.3. Clinical Safety Laboratory Assessments

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

8.2.4. Electronic Diary – Applicable Only to Substudies B, C, D, E, and F

Participants will be required to complete a reactogenicity e-diary through an application installed on a provisioned device or on the participant's own personal device. All participants will be asked to monitor and record local reactions, systemic events, and

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.

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

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

8.2.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.³⁹

8.2.4.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. 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 the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Local Reaction Grading Scale

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

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

8.2.4.3. Systemic Events

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 the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

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

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as an AE rather than as systemic events in the reactogenicity e-diary.

Potential COVID-19 symptoms that do not overlap with systemic events should be reported as AEs as per [Section 8.3](#).

8.2.4.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in [Table 4](#) during analysis.

If a fever of $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$) 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 $>40.0^{\circ}\text{C}$ ($>104.0^{\circ}\text{F}$). If a participant experiences a confirmed fever $>40.0^{\circ}\text{C}$ ($>104.0^{\circ}\text{F}$), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 4. Scale for Fever

$\geq 38.0\text{--}38.4^{\circ}\text{C}$ ($100.4\text{--}101.1^{\circ}\text{F}$)
$>38.4\text{--}38.9^{\circ}\text{C}$ ($101.2\text{--}102.0^{\circ}\text{F}$)
$>38.9\text{--}40.0^{\circ}\text{C}$ ($102.1\text{--}104.0^{\circ}\text{F}$)
$>40.0^{\circ}\text{C}$ ($>104.0^{\circ}\text{F}$)

8.2.4.5. Antipyretic/Analgesic Medication

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

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the [SoA](#), immediately before the administration of each 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.

8.3. 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 intervention (see [Section 7.1](#)).

During the active collection period as described in [Section 8.3.1](#), each participant/parent/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

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

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

For all participants, information about AEs will be collected for events occurring within approximately 1 month after each vaccination, and information about SAEs will be collected for events occurring approximately 6 months after each vaccination.

Substudy A

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 2, and from Visit 101 to Visit 102.

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to Visit 3 (approximately 6 months after the booster vaccination), and from Visit 101 to 103 (approximately 6 months after participants who originally received placebo are administered BNT162b2).

Substudy B

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 205 (1 month after Vaccination 2).

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

Substudy C

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 303 (1 month after the third dose).

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to Visit 304 (approximately 6 months after the participant’s last study vaccination).

Substudy D

For Cohorts 1 and 2, the time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 402 (1 month after the participant’s study vaccination) for Groups 1, 2b, 3, and 4, through and including Visit 403 for Group 2, and from Visit 404 through and including Visit 404b for Group 3 and Group 4 participants who receive a dose of BNT162b2 OMI at Visit 404.

For Group 5, the time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 504 (1 month after the participant’s second study vaccination), and from Visit 506 through Visit 507 (1 month after the participant’s third study vaccination).

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent through Visit 405 for Groups 1 to 4, and Visit 508 for Group 5 (approximately 6 months after the participant’s last study vaccination).

Substudy E

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 603 (1 month after the participant’s study vaccination).

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to Visit 605 (approximately 6 months after the participant’s study vaccination).

Substudy F

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 703 (1 month after the participant’s study vaccination).

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to Visit 705 (approximately 6 months after the participant's study vaccination).

For all participants, follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in [Section 8.3.1](#) are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in [Appendix 3](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. 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 8.3.1](#), 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.

8.3.2. 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.

8.3.3. 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 given in [Appendix 3](#).

8.3.4. 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.

8.3.5. 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 exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
 - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
 - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then 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 on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention. Beyond 28 days after the last dose of 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 using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

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

integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

- Spontaneous abortion including miscarriage and missed abortion;
- 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.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.5.3. Occupational Exposure

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

8.3.7.1. Substudies Including a Potential COVID-19 Illness Visit

The following substudies include a potential COVID-19 illness visit: Substudies A, D, E, and F.

Only for substudies including a potential COVID-19 illness visit, potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

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

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

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

OR

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

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

8.3.7.2. Substudies NOT Including a Potential COVID-19 Illness Visit

For substudies not including a potential COVID-19 illness visit, confirmed COVID-19 diagnoses will be considered AESIs (Section 8.3.8).

8.3.8. Adverse Events of Special Interest

The following events are considered AESIs:

- A confirmed diagnosis of myocarditis or pericarditis. See [Section 10.7.8.5.9](#) for Substudy A, [Section 10.8.8.3.6](#) for Substudy B, [Section 10.9.8.5](#) for Substudy C, [Section 10.10.8.6.7](#) for Substudy D, [Section 10.11.8.6.12](#) for Substudy E, and [Section 10.12.8.5.10](#) for Substudy F for additional procedures for monitoring of potential myocarditis or pericarditis.

8.3.8.1. Substudies NOT Including a Potential COVID-19 Illness Visit

This section provides information on AESIs that may be detected during the study:

- Confirmed COVID-19 diagnosis (clinical signs/symptoms and positive SARS-CoV-2 NAAT test)

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in [Sections 8.3.1](#) through [Section 8.3.4](#). 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 Reporting Form.

8.3.8.2. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication 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.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication 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 medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

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

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

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

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5. Genetics

8.5.1. Specified Genetics

For Substudies A, B, C, and F, genetics (specified analyses) are not evaluated.

For Substudies D and E, please see [Section 10.16](#).

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments are described in [Section 8.1](#).

8.8. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

9.1.1. Estimands

For estimands, refer to the respective appendix for each substudy. For Substudy A, refer to [Section 10.7.3](#). For Substudy B, refer to [Section 10.8.3](#). For Substudy C, refer to [Section 10.9.3](#). For Substudy D, refer to [Section 10.10.3](#). For Substudy E, refer to [Section 10.11.3](#). For Substudy F, refer to [Section 10.12.3](#).

9.1.2. Statistical Hypotheses

For Substudy A, refer to [Section 10.7.9.1.2](#) for hypotheses.

For Substudy B, refer to [Section 10.8.9.1.2](#) for hypotheses.

For Substudy C, refer to [Section 10.9.9.1.2](#) for hypotheses.

For Substudy D, refer to [Section 10.10.9.1.2](#) for hypotheses.

For Substudy E, refer to [Section 10.11.9.1.2](#) for hypotheses.

For Substudy F, refer to [Section 10.12.9.1.2](#) for hypotheses.

9.1.3. Multiplicity Adjustments

For Substudy A, refer to [Section 10.7.9.1.3](#) for multiplicity adjustments.

For Substudy B, refer to [Section 10.8.9.1.3](#) for multiplicity adjustments.

For Substudy C, refer to [Section 10.9.9.1.3](#) for multiplicity adjustments.

For Substudy D, refer to [Section 10.10.9.1.3](#) for multiplicity adjustments.

For Substudy E, refer to [Section 10.11.9.1.3](#) for multiplicity adjustments.

For Substudy F, refer to [Section 10.12.9.1.3](#) for multiplicity adjustments.

9.2. Analysis Sets

For 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](#).

For Substudy D, refer to [Section 10.10.9.2](#).

For Substudy E, refer to [Section 10.11.9.2](#).

For Substudy F, refer to [Section 10.12.9.2](#).

9.3. Statistical Analyses

The SAP will be developed and finalized for each substudy 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 general considerations of statistical analyses.

Refer to each substudy appendix for description of the statistical analyses for primary, secondary, and/or exploratory 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](#). For Substudy D, refer to [Section 10.10.9.3](#). For Substudy E, refer to [Section 10.11.9.3](#). For Substudy F, refer to [Section 10.12.9.3](#).

9.3.1. General Considerations

Each substudy will be reported separately.

CI 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 received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

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 populations 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. Missing serology data will not be imputed.

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy (mITT) population will be performed. Participants will be summarized according to the vaccine group to which they were randomized. Missing laboratory results will not be imputed.

9.3.1.1. Analyses for Binary Data

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

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

The 3-tier approach may be used to summarize AEs for certain substudies (refer to each substudy for specification). For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

9.3.1.2. Analyses for Continuous Data

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

9.3.1.2.1. Geometric Means

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

9.3.1.2.2. 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 Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.2.3. Geometric Mean Ratios

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

9.3.1.2.4. 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

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

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 (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her parent(s)/legal guardian(s) and answer all questions regarding the study. The participant or his/her parent(s)/legal guardian(s) 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 or their parent(s)/legal guardian(s) 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.

When consent is obtained from a participant's parent(s)/legal guardian(s), 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.

The investigator must ensure that each study participant or his/her parent(s)/legal guardian(s) 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 or his/her parent(s)/legal guardian(s) 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 or his/her parent(s)/legal guardian(s).

The participant or his/her parent(s)/legal guardian(s) 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 or his/her parent(s)/legal guardian(s) is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her 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 or their parent(s)/legal guardian(s) must be reconsented to the most current version of the ICD(s) during the participant's participation in the study.

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

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

10.1.4. Data Protection

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

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

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her 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.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee and Other Independent Oversight Committee

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

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the DMC 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, investigators, as appropriate.

Substudies E and F will also use an IRC that will be responsible for reviewing safety data as described in Sections [10.11.9.4.2](#) and [10.12.9.4.2](#).

Any further involvement of the DMC in each substudy is specified in the corresponding substudy appendix.

See [Section 10.7.9.4.2](#) for details of the DMC's role in Substudy A.

See [Section 10.8.9.4.1](#) for details of the DMC's role in Substudy B.

See [Section 10.9.9.4.2](#) for details of the DMC's role in Substudy C.

See [Section 10.10.9.4.2](#) for details of the DMC's role in Substudy D.

See [Section 10.11.9.4.2](#) for details of the DMC's role in Substudy E.

See [Section 10.12.9.4.2](#) for details of the DMC's role in Substudy F.

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, and/or www.pfizer.com, and other public registries 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

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data sharing

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

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 clinical study report.

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

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

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

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

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source data and its origin can be found in the study monitoring plan, which is maintained by the sponsor.

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

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

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

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

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. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

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

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

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor 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- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel 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 appropriately qualified medical personnel for study-related medical questions or problems, 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 investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

If required based on each substudy design and participant population, a pregnancy test will be performed at times defined in the [SoA](#) section of each substudy.

- 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. Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition
<ul style="list-style-type: none">• 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
<ul style="list-style-type: none">• 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:<ul style="list-style-type: none">• 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 either an increase in 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.

<p>d. Results in persistent or significant disability/incapacity</p> <ul style="list-style-type: none"> 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.
<p>e. Is a congenital anomaly/birth defect</p>
<p>f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.</p> <ul style="list-style-type: none"> 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.
<p>g. Other situations:</p> <ul style="list-style-type: none"> 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
<p>The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the Vaccine SAE Reporting Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs;</p>

(2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs or SAEs associated with exposure during pregnancy or breastfeeding 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 non-participant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

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

Assessment of Intensity

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

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

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 his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has 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 his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool 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 data collection tool 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 Vaccine SAE Reporting Form

- Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

The following appendix applies as specified in each substudy eligibility criteria section.

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 with a female of childbearing potential 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 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in [Section 10.4.4](#)).

10.4.2. Female Participant Reproductive Inclusion Criteria

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 using an acceptable contraceptive method as described below 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:
3. Documented hysterectomy;
4. Documented bilateral salpingectomy;
5. Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate 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.

- 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 nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they 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.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion (eg, bilateral tubal ligation).
5. Vasectomized partner:
 - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential 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.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
 - Oral;
 - Intravaginal;
 - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
 - Oral;
 - Injectable.
8. Sexual abstinence:
 - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
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: 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 $3 \times \text{ULN}$ 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 Tbili elevations ($>2 \times \text{ULN}$) by several days or weeks. The increase in Tbili typically occurs while AST/ALT is/are still elevated above $3 \times \text{ULN}$ (ie, AST/ALT and Tbili values will be elevated within the same laboratory sample). In rare instances, by the time Tbili 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 Tbili 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 Tbili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times \text{ULN}$ AND a Tbili value $>2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $<2 \times \text{ULN}$ or not available.
- For participants with baseline AST OR ALT OR Tbili 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 $>3 \times \text{ULN}$; or $>8 \times \text{ULN}$ (whichever is smaller).
- Preexisting values of Tbili above the normal range: Tbili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ or if the value reaches $>3 \times \text{ULN}$ (whichever is smaller).

Rises in AST/ALT and Tbili 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 Tbili 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 Tbili 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.

10.6. Appendix 6: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual (including the lifting of any quarantines and travel bans/advisories).

10.6.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- 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 [Appendix 4](#).

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

10.7. Appendix 7: Substudy A

10.7.1. Substudy Summary

10.7.1.1. Synopsis

See [Section 1.1](#) for a synopsis of Substudy A.

10.7.1.2. Schema

	Visit Number	1	2	3	4	Unplanned
	Visit Description	Booster Vaccination	1-Month Telephone Contact	6-Month Follow-Up Visit	12-Month Telephone Contact	Potential COVID-19 Illness Visit
Participants having received 2 prior doses of 30 µg BNT162b2 at least 6 months prior to randomization	Group 1 (n=5000)	BNT162b2				
	Group 2 (n=5000)	Placebo				
	Blood draw	20 mL		20 mL		

Visit Number	101	102	103	Unplanned
Visit Description	BNT162b2 Vaccination	1-Month Telephone Contact 2	6-Month Telephone Contact	Potential COVID-19 Illness Visit
Group 2	BNT162b2			
Blood Draw	20 mL			

10.7.1.3. Schedule of Activities for Substudy A

Visit Number	1	2	3	4	Unplanned
Visit Description	Booster Vaccination	1-Month Telephone Contact	6-Month Follow-Up Visit ^a	12-Month Telephone Contact ^a	Potential COVID-19 Illness Visit ^b
Visit Window	Day 1 ^c	28 to 35 Days After Visit 1	175 to 189 Days After Visit 1	350 to 378 Days After Visit 1	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Obtain informed consent	X				
Obtain the participant's prior participant number from Study C4591001	X				
Assign participant number	X				
Obtain demography and medical history data	X				
Perform clinical assessment ^d	X				
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X	X	X	
Measure height and weight	X				
Measure temperature (body)	X				
Perform urine pregnancy test (if appropriate)	X				
Confirm use of contraceptives (if appropriate)	X	X			
Collect nonstudy vaccine information	X	X			
Collect prohibited medication use		X	X	X	X
Confirm eligibility	X				
Review temporary delay criteria	X				
Collect blood sample for immunogenicity assessment	~20 mL		~20 mL		
Obtain nasal (midturbinate) swab	X				X
Obtain randomization number and study intervention allocation	X				
Administer study intervention	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X				
Explain participant communication methods, assist the participant with downloading the app, or issue provisioned device, if required	X				

Visit Number	1	2	3	4	Unplanned
Visit Description	Booster Vaccination	1-Month Telephone Contact	6-Month Follow-Up Visit ^a	12-Month Telephone Contact ^a	Potential COVID-19 Illness Visit ^b
Visit Window	Day 1 ^c	28 to 35 Days After Visit 1	175 to 189 Days After Visit 1	350 to 378 Days After Visit 1	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Provide/ensure the participant has a thermometer	X				
Request the participant return the e-diary or assist the participant to delete the application				X	
Collect AEs and SAEs as appropriate	X	X	X ^e		X ^f
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)					X
Contact the participant by telephone		X		X	

- This visit will be conducted for all participants if the study remains blinded at the time of the visit or, if the study has been unblinded, for participants who originally received BNT162b2 or placebo recipients who declined BNT162b2 booster vaccination.
- The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
- The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
- Including, if indicated, a physical examination.
- Any AEs occurring up to 48 hours after the blood draw must be recorded (see [Section 8.3.1](#)).
- AEs need only be recorded if the participant remains in the AE reporting period (see [Section 8.3.1](#)).

10.7.1.3.1. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who originally received placebo will have the opportunity to receive BNT162b2 as part of the study either indicated by, and at a time informed by, the outcome of the interim analyses detailed in [Section 10.7.9.4](#) or at a time decided at the discretion of the sponsor.

Visit Number Visit Description	101 BNT162b2 Vaccination	102 1-Month Telephone Contact 2	103 6-Month Telephone Contact	Unplanned Potential COVID-19 Illness Visit
Visit Window	As Informed by the Outcome of the Interim Analyses, or at the Discretion of the Sponsor	28 to 35 Days After Visit 101	175 to 189 Days After Visit 101	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Confirm participant originally received placebo	X			
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X	X	
Perform urine pregnancy test (if appropriate)	X			
Confirm use of contraceptives (if appropriate)	X			
Collect prohibited medication use	X	X	X	X
Confirm eligibility	X			
Review temporary delay criteria	X			
Collect blood sample for immunogenicity assessment	~20 mL			
Obtain nasal (midturbinate) swab	X			X
Obtain vaccine vial allocation via IRT	X			
Administer BNT162b2	X			
Assess acute reactions for at least 30 minutes after study intervention administration	X			
Request the participant return the e-diary or assist the participant to delete the application			X	
Collect AEs and SAEs as appropriate	X	X	X	X ^a
Collection of COVID-19-related clinical and laboratory information (including local diagnosis)				X
Contact the participant by telephone		X	X	

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

a. AEs need only be recorded if the participant remains in the AE reporting period (see [Section 8.3.1](#)).

10.7.2. Introduction

10.7.2.1. Study Rationale

Substudy A will evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2 when administered to participants having previously received 2 doses of BNT162b2 at least 6 months prior to randomization.

10.7.2.2. Background

See [Section 2.2](#) for the study background.

10.7.2.3. Benefit/Risk Assessment

No additional risks are identified for Substudy A beyond those detailed for the master study (see [Section 2.3](#)).

10.7.2.3.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy A may be:

- Receipt of a booster dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic.
- Access to COVID-19 diagnostic testing.
- Contributing to research to help others in a time of global pandemic.

10.7.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Efficacy	Primary Efficacy	Primary Efficacy
To describe the efficacy of a booster dose of BNT162b2 against confirmed COVID-19 occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed COVID-19 occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

Objectives	Estimands	Endpoints
Primary Safety	Primary Safety	Primary Safety
To define the safety profile of a booster dose of BNT162b2	In participants receiving 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> • AEs from the booster dose to 1 month after the booster dose • SAEs from the booster dose to 6 months after the booster dose 	<ul style="list-style-type: none"> • AEs • SAEs
Secondary Efficacy	Secondary Efficacy	Secondary Efficacy
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on FDA definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on FDA definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on CDC definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on CDC definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
Exploratory		
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received the BNT162b2 booster dose	In participants who received BNT162b2 at the booster vaccination (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	Confirmed COVID-19 incidence per 1000 person-years of follow-up

10.7.4. Study Design

10.7.4.1. Overall Design

This is a Phase 3 randomized, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥ 16 years of age who have completed a 2-dose primary series of BNT162b2 at least 6 months prior to randomization will be enrolled, and participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo as shown in [Section 10.7.1.2](#). Randomization will be stratified by age, such that approximately 60% of participants enrolled will be ≥ 16 to 55 years of age and approximately 40% of participants >55 years of age. Approximately 10,000 participants will be randomized in the study. Assuming a 15% nonevaluable rate, there will be approximately 4250 evaluable participants in each group.

Participants who are randomized to receive placebo at the booster vaccination visit will be offered the opportunity to receive BNT162b2 if indicated by the outcome of the interim analyses, as outlined below in [Section 10.7.4.2.1](#) and further detailed in [Section 10.7.9.4](#), or at the discretion of the sponsor. The timing of this booster vaccination may be informed by the outcome of the interim analyses detailed in [Section 10.7.9.4](#) or at a time decided by the sponsor.

The study may be terminated early, for reasons including (but not limited to) access to and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial. Further to this, participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program will be discontinued from this study.

10.7.4.2. Scientific Rationale for Substudy A Design

See [Section 10.7.2.1](#).

10.7.4.2.1. Statistical Rationale for Substudy A Design

In addition to assessing the safety of administering a booster dose in a large number of participants, a key objective of this study is to characterize the potential for waning VE over time in participants who do not receive a booster. It is important to identify when a booster is needed to protect the participants in this trial, as well as to inform vaccine policy decision-makers. Consequently, the most appropriate statistical framework to facilitate decision-making in this setting is periodic statistical summaries (every 2 months over the scheduled 6-month follow-up period) using statistical guidelines, rather than the traditional hypothesis testing framework with strong control of overall type 1 error across analysis time points.

Using a traditional hypothesis testing framework, a policy of recommending a booster would be implemented only if the lower limit of the alpha-adjusted CI for VE of the boosted group relative to the unboosted group was greater than some specified value (eg, 20% or 30%). This approach controls the overall type 1 error, that is, deciding that a booster is necessary to maintain VE when it is actually not necessary. But strong control of type 1 error inflates type

2 error for a fixed sample size. And in this setting, type 2 error, that is, deciding that a booster is not necessary when it actually is, has a greater negative impact on public health.

For this reason, a descriptive statistical approach will be used with point estimates of VE (boosted relative to unboosted) and unadjusted (for multiplicity) 95% CIs at each time point (2, 4, and 6 months). In addition, to help put these results into perspective, an inferred VE for the unboosted group (relative to an unvaccinated population) will be calculated. Specifically, assuming that the newly boosted group has the same VE (relative to an unvaccinated population) over time that was observed in the parent C4591001 trial, an inferred unvaccinated (placebo) disease rate can be obtained at various time points and used to calculate the inferred VE (relative to unvaccinated) for the unboosted group. If this value is lower than a specified value (eg, 60%) at a given analysis time point, then a decision to offer a booster to the unboosted participants at that time may be implemented.

10.7.4.2.2. Diversity of Study Population

Reasonable attempts will be made to enroll participants with the distribution of characteristics shown to reflect that achieved in C4591001.⁴⁰

10.7.4.3. Justification for Dose

See [Section 4.3](#) for a justification of the BNT162b2 dose used in Substudy A.

10.7.4.4. End of Study Definition

See [Section 4.4](#).

10.7.5. Study Population

Details of the master eligibility criteria are shown in [Section 5](#). Participants must meet all of the general inclusion and exclusion criteria as specified for both the master protocol and Substudy A–specific inclusion and exclusion criteria.

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. Male or female participants ≥ 16 years of age at Visit 1 (Day 1) who participated in Study C4591001.

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

Type of Participant and Disease Characteristics:

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

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

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in [Section 10.15](#).

Informed Consent:

4. Capable of giving personal signed informed consent/assent, have parent(s)/legal guardian capable of giving signed informed consent as described in [Appendix 1](#), 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/electronically signed informed consent (and assent) from each study participant's legal guardian (as defined in [Appendix 1](#)), and the participant's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

Other Inclusions:

5. Participants who have received 2 prior doses of 30 µg BNT162b2 19 to 42 days apart, with the second dose being at least 175 days before Visit 1 (Day 1).

Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

10.7.5.2. Exclusion Criteria

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

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

3. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.
4. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
5. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥ 14 days at a dose of ≥ 20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. Prior receipt of any COVID-19 vaccine other than BNT162b2.

Other Exclusions:

10. Investigator site staff or Pfizer-BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
11. Receipt of medications intended to prevent COVID-19.
12. Prior receipt of more than 2 doses of BNT162b2 30 μ g.
13. Participation in other studies involving study intervention within 28 days prior to study entry, other than C4591001, and/or within 28 days of confirmed receipt of BNT162b2 within the study.

10.7.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy A as detailed in [Section 5.3](#) and [Section 10.4](#).

10.7.5.4. Screen Failures

See [Section 5.4](#).

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

See [Section 5.5](#).

10.7.6. Study Intervention(s) and Concomitant Therapy

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

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

10.7.6.1. Study Intervention(s) Administered

See [Section 6.1](#) for details of BNT162b2.

Additional Intervention Name	Saline Placebo
Type	Placebo
Dose Formulation	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	N/A
Dosage Level(s)	N/A
Route of Administration	Intramuscular injection
Use	Placebo
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

10.7.6.1.1. Administration

Participants will receive 1 dose of study intervention at Visit 1 in accordance with the substudy's SoA ([Section 10.7.1.3](#)).

Study intervention at the booster vaccination visit should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Study intervention administration at Visit 101 will be conducted in an open-label manner.

10.7.6.1.2. Preparation and Dispensing

For booster vaccination during Substudy A, study intervention will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way as to ensure that the participants remain blinded.

10.7.6.2. Measures to Minimize Bias: Randomization and Blinding

10.7.6.2.1. Blinding of Site Personnel

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

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The study will be unblinded to site personnel at a time informed by the outcome of the interim analyses, as detailed in [Section 10.7.9.4](#), or at a time decided by the sponsor.

10.7.6.2.2. Blinding of the Sponsor

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

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

- An unblinded team supporting interactions with, and analyses for, the DMC (see [Section 10.7.9.4.2](#)). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received.
- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.
- After the study data used for submission become public, the blinded study team will also have access to those data and become unblinded at a group level.
- The study will be unblinded to all sponsor/Pfizer staff at a time informed by the outcome of the interim analyses, as detailed in [Section 10.7.9.4](#), or at a time decided by the sponsor.

10.7.6.2.3. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

10.7.6.3. Study Intervention Compliance

See [Section 6.4](#).

10.7.6.4. Dose Modification

See [Section 6.5](#).

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

See [Section 6.6](#).

10.7.6.6. Treatment of Overdose

See [Section 6.7](#).

10.7.6.7. Concomitant Therapy

See [Section 6.8](#).

10.7.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See [Section 7](#).

10.7.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 60 mL.

For all participants, other 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 60 consecutive days.

10.7.8.1. Efficacy and/or Immunogenicity Assessments for Substudy A

10.7.8.1.1. Efficacy Against COVID-19

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see [Section 10.7.8.5.5.1](#)), for the purposes of the study he or she will be considered to potentially have COVID-19 illness. 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 and Pfizer-validated), 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 10.7.8.5.5.1](#)) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

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

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
 - Fever;
 - New or increased cough;
 - New or increased shortness of breath;
 - Chills;
 - New or increased muscle pain;
 - New loss of taste or smell;
 - Sore throat;
 - Diarrhea;
 - Vomiting.
- Confirmed severe COVID-19 (FDA definition⁴¹): confirmed COVID-19 and presence of at least 1 of the following:
 - Clinical signs at rest indicative of severe systemic illness (RR \geq 30 breaths per minute, HR \geq 125 beats per minute, SpO₂ \leq 93% on room air at sea level, or PaO₂/FiO₂ $<$ 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 definition⁴²): 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.

10.7.8.2. Safety Assessments

See [Section 8.2](#).

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

See [Section 8.3](#).

10.7.8.4. Immunogenicity Assessments

See [Section 8.1](#).

10.7.8.5. Substudy A Procedures

10.7.8.5.1. Visit 1 – Booster Vaccination (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant 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/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior participant number from Study C4591001 and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical

examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.

- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.
- Explain the e-diary technologies available for this study (see [Section 10.7.8.5.6](#)), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.

- Provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, 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 10.7.8.5.6](#) for further details.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.7.8.5.9](#)).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, 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, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.7.8.5.5](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

10.7.8.5.2. Visit 2 – 1-Month Telephone Contact (28 to 35 Days After Visit 1)

- Record AEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in [Section 5.3](#).
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.7.8.5.9](#)).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, 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, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.7.8.5.5](#).
- 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.

10.7.8.5.3. Visit 3 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 1)

This visit will be conducted for all participants if the study remains blinded at the time of the visit or, if the study has been unblinded, for participants who originally received BNT162b2 or placebo recipients who declined the BNT162b2 booster vaccination.

- Record SAEs as described in [Section 8.3](#).
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 2 (if any).
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.7.8.5.5](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.7.8.5.4. Visit 4 – 12-Month Telephone Contact (350 to 378 Days After Visit 1)

- This visit will be conducted for all participants if the study remains blinded at the time of the visit or, if the study has been unblinded, for participants who originally received BNT162b2 or placebo recipients who declined the BNT162b2 booster vaccination.
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect the participant's e-diary or assist the participant in removing the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.7.8.5.5. COVID-19 Surveillance (All Substudy A Participants)

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

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

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs.

Participants may utilize a COVID-19 illness e-diary through an application (see [Section 10.7.8.5.6](#)) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

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

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant 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:

- Record AEs, as appropriate as described in [Section 8.3](#). Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if the visit is conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship 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 \geq 30 breaths per minute, HR \geq 125 beats per minute, SpO₂ \leq 93% on room air at sea level, or PaO₂/FiO₂ <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 C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.7.8.5.6. Communication and Use of Technology

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

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).

- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

10.7.8.5.7. SARS-CoV-2 NAAT Results

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

- Visit 1 and Visit 101: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection.
- 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 Visit 1 and Visit 101 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

10.7.8.5.8. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who are randomized to receive placebo at the booster vaccination visit will be offered the opportunity to receive BNT162b2 if indicated by the outcome of the interim analysis, as detailed in [Section 10.7.9.4](#), or at the discretion of the study sponsor. The timing of this booster vaccination may be informed by the outcome of the interim analyses or at a time decided by the sponsor.

10.7.8.5.8.1. Visit 101 – BNT162b2 Vaccination

- Unblind the participant's study intervention assignment (if information not already available), and confirm the participant originally received only placebo at the booster vaccination visit. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3.1](#).

- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria and exclusion criteria prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 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.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.7.8.5.9](#)).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, 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, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.7.8.5.5](#).
- 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 and the dispenser/administrator updates the study intervention accountability records.

10.7.8.5.8.2. Visit 102 – 1-Month Telephone Contact 2 (28 to 35 Days After Visit 101)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in [Section 8.3](#).
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.7.8.5.9](#)).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, 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, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.7.8.5.5](#).
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.7.8.5.8.3. Visit 103 – 6-Month Telephone Contact (175 to 189 Days After Visit 101)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in [Section 8.3](#).
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 102 (if any).
- Collect the participant's e-diary or assist the participant in removing the study application from his or her own personal device.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

10.7.8.5.9. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably 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.

10.7.9. Statistical Considerations for Substudy A

See [Section 9](#) for master protocol statistical considerations and substudy specifics below.

10.7.9.1. Statistical Hypotheses

10.7.9.1.1. Estimands

The estimands corresponding to the primary, secondary, and exploratory objectives are described in the table in [Section 10.7.3](#).

In the primary safety objective evaluations, 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 efficacy objectives are based on the evaluable efficacy population ([Section 10.7.3](#)). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed for the all-available efficacy populations. Missing laboratory results will not be imputed.

10.7.9.1.2. Statistical Hypotheses

All objectives in this substudy are descriptive. No hypothesis testing is planned.

10.7.9.1.3. 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, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable efficacy	All eligible randomized participants who receive the booster vaccination as randomized and have no other important protocol deviations as determined by the clinician.
All-available efficacy (mITT)	All randomized participants who receive at least 1 dose of the study intervention.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

10.7.9.3. Statistical Analyses

The SAP will be developed and finalized for this substudy before any analyses are performed and will describe the analyses and procedures for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary 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
Efficacy	<p>Ratio of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group</p> <p>VE will be estimated by $100 \times (1 - \text{IRR})$, where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the booster dose. The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method adjusting for surveillance time.</p> <p>In addition, a summary of VE over different time intervals (ie, prior to 2 months, from 2 months to 4 months, and from 4 months to 6 months after the booster dose, etc.), along with the associated 2-sided 95% CI, will be calculated using the same method.</p> <p>Ratio of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group</p> <p>The point estimate of VE and the associated 2-sided 95% CI, including VE at different time intervals, will be calculated using the same method as for the first primary endpoint described above.</p>
Safety	<p>AEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs from the booster dose to 1 month after the booster dose will be provided for each vaccine group. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA</p>

Endpoint	Statistical Analysis Methods
	<p>preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. Analyses methods are described in Section 9.3.1.1.</p> <p>SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from the booster dose to 6 months after the booster dose will be provided for each vaccine group.</p>

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

Endpoint	Statistical Analysis Methods
Efficacy	<p>Ratio of confirmed severe COVID-19 illness (based on FDA definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group</p> <p>Ratio of confirmed severe COVID-19 illness (based on FDA definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group</p> <p>Ratio of confirmed severe COVID-19 illness (based on CDC definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group</p> <p>Ratio of confirmed severe COVID-19 illness (based on CDC definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group</p> <p>For each of the above efficacy endpoints, the point estimate of VE and the associated 2-sided 95% CI for VE will be calculated using the same method as for the first primary endpoint described above.</p>

10.7.9.3.4. Exploratory Endpoint(s)

Endpoint	Statistical Analysis Methods
Efficacy	<p>Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at the booster vaccination</p> <p>Incidence rates (per 1000 person-years of follow-up) and 2-sided 95% CIs based on Poisson distribution for confirmed COVID-19 illness from 7 days after the booster dose will be provided for participants who received BNT162b2 at initial randomization and subsequently, respectively.</p>

10.7.9.4. Interim Analyses

In this substudy, interim efficacy analyses were originally planned to be performed every 2 months by an unblinded statistical team to inform the timing of administration of BNT162b2 to those originally assigned to placebo. This substudy has been unblinded after the first interim analysis as informed by the outcome of the analysis; follow-up interim analyses are no longer applicable. The first interim analysis was performed after all participants reach 2 months of blinded follow-up. The final efficacy analyses to assess the primary and secondary efficacy objectives are planned to be conducted using complete blinded follow-up period data.

At each interim analysis, the following 2 estimates of VE will be obtained: (1) VE of the BNT162b2 booster group to the nonbooster group (placebo), which is the primary estimand defined for this substudy and directly estimable using the data observed in this substudy, and (2) VE of the nonbooster group (who received a primary series of 2 doses of BNT162b2 approximately 6 months prior to enrollment in this study and did not receive the BNT162b2 booster) relative to an unvaccinated population (never received a BNT162b2 primary series, not observable in this study). These estimates will be obtained using the following derivations.

Let VE_{12} be the VE of the BNT162b2 booster group relative to the nonbooster group, VE_1 be the VE of the BNT162b2 booster group relative to an unvaccinated population, VE_2 be the VE of the nonbooster group relative to an unvaccinated population, IR_1 be the incidence rate of COVID-19 illness in the BNT162b2 booster group, IR_2 be the incidence rate of COVID-19 illness in the placebo booster group, and IR_0 be the nonobservable incidence rate in the unvaccinated population;

(1) VE_{12} can be estimated by observed IR_1 and IR_2 in the study as $VE_{12} = 1 - \frac{IR_1}{IR_2}$;

Since $VE_1 = 1 - \frac{IR_1}{IR_0}$, $VE_2 = 1 - \frac{IR_2}{IR_0}$,

(2) VE_2 can then be estimated by observed IR_1 and IR_2 in the study and an assumed VE_1 as

$$VE_2 = 1 - \frac{IR_2(1-VE_1)}{IR_1}.$$

Although VE_1 is also not observable from the study, it is expected that VE after the booster dose will be similar to that after the first 2 vaccine doses. Based on the results of the updated efficacy analyses from Study C4591001, the VE from 7 days to 2 months, from 2 to 4 months, and from 4 to 6 months after Dose 2 were approximately 96%, 90%, and 84%, respectively. After 6 months, a 6% drop in VE every 2 months will be assumed. These assumed values of VE_1 will be used to estimate VE_2 at the interim analyses.

If the point estimate of VE_2 (nonbooster group relative to unvaccinated population) in a 2-month interval (ie, 7 days to 2 months, 2 to 4 months, etc.) at the interim analysis is <60%, the study will be unblinded and the placebo group participants may receive BNT162b2 earlier than approximately 175 days after the vaccination at Visit 1. If VE_2 remains $\geq 60\%$ at the interim analyses, all participants may remain blinded in the study and placebo recipients may not be offered BNT162b2 booster until the 12-month visit. In addition, the placebo group participants may not receive BNT162b2 as part of the study if VE_2 is $\geq 60\%$ at the final analysis.

10.7.9.4.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Interim efficacy analyses after all participants reach 2 months of blinded follow-up;
- Efficacy and safety analysis at the end of the study.
- Additional analyses may be conducted if required for regulatory purposes.

10.7.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

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

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after the booster vaccination
- Contemporaneous review of all SAEs up to 6 months after the booster vaccination
- At the time of the planned interim analyses, and ad hoc if requested by the unblinded team, review of COVID-19 cases for an adverse imbalance of COVID-19 cases and/or severe COVID-19 cases between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

10.7.9.5. Sample Size Determination

The sample size of the study is determined to accrue sufficient COVID-19 cases for the VE assessment. Assuming a 15% nonevaluable rate, with 10,000 participants randomized in a 1:1 ratio to receive BNT162b2 booster or placebo, there will be approximately 4250 evaluable participants in each group. Table 5 presents assumptions of VE at various time intervals after the booster dose and the expected number of COVID-19 cases within each time interval with 4250 evaluable participants in each group. If the underlying incidence rate in the unvaccinated population is 0.14 per person-year follow-up, the study will accrue approximately 127 cases in 6 months. If, due to vaccination rollout and other public health measures, the incidence rate drops by 50%, approximately 63 cases are expected to be accrued in 6 months.

Table 5. Expected Number of COVID-19 Cases Under Assumed Vaccine Efficacy and Incidence Rate

Follow-Up Time Postbooster	Assumed VE			Expected Number of Cases With 4250 Evaluable Participants Per Group			
	VE ₁	VE ₂	VE ₁₂	IR ₀ = 0.14/pyr		IR ₀ = 0.07/pyr	
				Boosted	Nonboosted	Boosted	Nonboosted
7 Days to 2 months	96%	72%	85.7%	3	24	2	12
2 to 4 Months	90%	66%	70.6%	10	34	5	17
4 to 6 Months	84%	60%	60.0%	16	40	8	20
7 Days to 4 months	92.8%	68.8%	76.9%	13	58	7	29
7 Days to 6 months	89.8%	65.8%	70.2%	29	98	15	49

Abbreviations: IR₀ = assumed underlying incidence rate in unvaccinated population. The observed incidence rate in placebo group of study C4591001 was 0.14 per person-year follow-up; pyr = person-years;

VE₁ = vaccine efficacy of BNT162b2 booster group relative to unvaccinated population, assumed to be similar to the vaccine efficacy after the primary vaccination series observed in Study C4591001;

VE₂ = vaccine efficacy of nonbooster group relative to unvaccinated population, assumed to have 6% drop every 2 months after the primary vaccination series and the average time after primary vaccination series at study entry is approximately 8 months for participants enrolled in this substudy;

VE₁₂ = vaccine efficacy of BNT162b2 booster group to nonbooster group, calculated by $VE_{12} = 1 - (1 - VE_1) / (1 - VE_2)$.

Table 6 shows the probability to show the lower limit of the 95% CI for VE >30% for a given number of cases observed in the study under various assumed values of VE. For example, if the VE of the booster group relative to the nonbooster group is 70% over 6 months of blinded follow-up, 70 cases will provide 88.9% probability to show that the lower limit of the 95% CI for VE is >30%.

Table 6. Probability for Vaccine Efficacy Assessment

Assumed True VE	Probability to Show Lower Limit of 95% CI for VE >30% With Given Total Number of Cases				
	30 cases	50 cases	70 cases	90 cases	110 cases
60%	0.204	0.411	0.560	0.666	0.744
65%	0.306	0.579	0.743	0.842	0.902
70%	0.443	0.750	0.889	0.950	0.978
75%	0.607	0.889	0.970	0.992	0.998
80%	0.777	0.969	0.996	>0.999	>0.999

For safety outcomes, Table 7 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 0.1%, with 5000 participants in a vaccine group, there is 99% probability of observing at least 1 AE.

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

Sample Size (N)	Assumed True Event Rate of an AE							
	0.01%	0.05%	0.1%	0.2%	0.5%	1%	2%	5%
5000	0.39	0.92	0.99	>0.99	>0.99	>0.99	>0.99	>0.99

10.8. Appendix 8: Substudy B

10.8.1. Substudy Summary

10.8.1.1. Synopsis

See [Section 1.1](#) for a synopsis of Substudy B.

10.8.1.2. Schema

	Visit Number	201	202	203	204	205
	Visit Description	Vaccination 1	4-Day Follow-Up Visit (After Vaccination 1)	Vaccination 2	4-Day Follow-Up Visit (After Vaccination 2)	1-Month Follow-Up Visit (After Vaccination 2)
Participants having received 2 or 3 prior doses of 30 µg BNT162b2, with their last dose at least 4 months (120 days) prior to randomization	Sequence 1 (n=750)	BNT162b2		Placebo		
	Sequence 2 (n=750)	Placebo		BNT162b2		
	Blood draw	10 mL	10 mL	10 mL	10 mL	10 mL

10.8.1.3. Schedule of Activities for Substudy B

Visit Number	201	202	203	204	205
Visit Description	Vaccination 1	4-Day Follow-Up Visit (After Vaccination 1)	Vaccination 2	4-Day Follow-Up Visit (After Vaccination 2)	1-Month Follow-Up Visit (After Vaccination 2)
Visit Window	Day 1 ^a	2-5 Days After Visit 201	28-35 Days After Visit 201	2-5 Days After Visit 203	28-35 Days After Visit 203
Confirm that the participant has received 2 or 3 prior doses of BNT162b2, with their last dose at least 4 months (120 days) prior to randomization; secondary confirmation by another site staff member is required	X				
Obtain informed consent/assent ^b	X				
Obtain the participant's prior study and participant number (if applicable)	X				
Assign participant number	X				
Obtain demography and medical history data	X				
Perform clinical assessment ^c	X				
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X		X
Measure height and weight	X				
Measure temperature (body)	X		X		
Perform urine pregnancy test (if appropriate)	X		X		
Confirm use of contraceptives (if appropriate)	X	X	X	X	
Collect nonstudy vaccine information	X	X	X	X	X
Collect prohibited medication use		X	X	X	X
Confirm eligibility	X		X		
Review temporary delay criteria	X		X		
Collect blood sample	~10 mL	~10 mL	~10 mL	~10 mL	~10 mL
Obtain randomization number	X				
Obtain study intervention allocation	X		X		
Administer study intervention	X		X		
Assess acute reactions for at least 30 minutes after study intervention administration	X		X		

Visit Number	201	202	203	204	205
Visit Description	Vaccination 1	4-Day Follow-Up Visit (After Vaccination 1)	Vaccination 2	4-Day Follow-Up Visit (After Vaccination 2)	1-Month Follow-Up Visit (After Vaccination 2)
Visit Window	Day 1 ^a	2-5 Days After Visit 201	28-35 Days After Visit 201	2-5 Days After Visit 203	28-35 Days After Visit 203
Explain/review participant communication methods (including for reactogenicity e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X		X		
Provide/ensure participant has a thermometer and measuring device	X		X		
Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration)	X →	X →	X →	X →	X
Review ongoing reactogenicity e-diary symptoms with participant and obtain and record stop dates		X	X	X	X
Collect the e-diary device or assist the participant to delete the application					X
Collect AEs and SAEs as appropriate	X	X	X	X	X ^d
Contact the participant by telephone					

Abbreviation: HIV = human immunodeficiency virus.

- The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
- 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).
- Including, if indicated, a physical examination.
- Any AEs occurring up to 48 hours after the blood draw must be recorded (see [Section 8.3.1](#)).

10.8.2. Introduction

10.8.2.1. Study Rationale

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 after the second dose of the vaccine, and within 14 days after vaccination. These events are generally mild, and individuals tend to recover within a short time following standard treatment and rest. However, the incidence of subclinical myocarditis and pericarditis prior to the presentation of overt clinical signs and symptoms is unknown. Therefore, this protocol's Substudy B will assess the safety and tolerability of a single dose of BNT162b2 as compared to placebo control, through the potential analysis of serum troponin levels, in participants ≥ 12 and ≤ 30 years of age who have received 2 or 3 prior doses of BNT162b2 (30- μ g doses), with their last dose at least 4 months (120 days) prior to randomization.

10.8.2.2. Background

See [Section 2.2](#) for the study background.

10.8.2.3. Benefit/Risk Assessment

No additional risks are identified for Substudy B beyond those detailed for the master study (see [Section 2.3](#)).

10.8.2.3.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy B may be:

- Receipt of a booster (third or fourth) dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic.
- Contributing to research to help others in a time of global pandemic.

10.8.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety	Primary Safety	Primary Safety
To describe the frequency of elevated troponin I levels before and after a booster dose of BNT162b2 or placebo	In participants receiving 1 dose of study intervention, the percentage of participants with elevated troponin I levels before and at subsequent time points after a booster dose of BNT162b2 or placebo	<ul style="list-style-type: none"> Troponin I level
To define the safety profile of a booster dose of BNT162b2	In participants receiving 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> Local reactions for up to 7 days following each vaccination Systemic events for up to 7 days following each vaccination AEs within 1 month after each vaccination SAEs within 1 month after each vaccination 	<ul style="list-style-type: none"> Local reactions (pain at the injection site, redness, and swelling) Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) AEs SAEs

10.8.4. Study Design

10.8.4.1. Overall Design

This is a randomized, placebo-controlled, observer-blind, crossover substudy to evaluate the safety and tolerability of a booster (third or fourth) dose of BNT162b2. Participants ≥ 12 years of age to ≤ 30 years of age who have received 2 or 3 prior doses of BNT162b2 (30- μ g doses), with their last dose at least 4 months (120 days) prior to randomization, will be enrolled. Participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo at Visit 201 and the alternative at Visit 203, four weeks later. Randomization will be stratified by age (stratified as 12-17, 18-24, and 25-30 years of age). Approximately 1500 participants will be randomized in the study. A blood sample will be collected to obtain a serum sample for troponin testing before each administration of blinded study intervention, 2 to 5 days after each administration, and 1 month after the second administration.

10.8.4.2. Scientific Rationale for Substudy B Design

See [Section 10.8.2.1](#).

10.8.4.2.1. Diversity of Study Population

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

10.8.4.3. Justification for Dose

See [Section 4.3](#) for a justification of the BNT162b2 dose used in Substudy B.

10.8.4.4. End of Study Definition

See [Section 4.4](#).

10.8.5. Study Population

Details of the master eligibility criteria are shown in [Section 5](#). Participants must meet all of the general inclusion and exclusion criteria as specified for both the master protocol and Substudy B-specific inclusion and exclusion criteria.

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. Male or female participants 12 to 30 years of age, inclusive, who have received 2 or 3 prior doses of 30 µg BNT162b2 (with the first 2 doses 19 to 60 days apart), with the last dose being at least 4 months (120 days) before Visit 1 (Day 1).

Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

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

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in [Section 10.15](#).

Informed Consent:

4. Capable of giving personal signed informed consent/assent, have parent(s)/legal guardian capable of giving signed informed consent as described in [Appendix 1](#), 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/electronically signed informed consent (and assent) from each study participant's legal guardian (as defined in [Appendix 1](#)), and the participant's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

10.8.5.2. Exclusion Criteria

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

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
3. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.
4. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
5. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥ 14 days at a dose of ≥ 20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study.

Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. Prior receipt of any COVID-19 vaccine other than BNT162b2.

Other Exclusions:

10. Investigator site staff or Pfizer-BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
11. Receipt of medications intended to prevent COVID-19.
12. Prior receipt of more than 3 doses of BNT162b2 30 µg.
13. Participation in other studies involving study intervention within 28 days prior to study entry through and including 28 days after the last dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

10.8.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy B as detailed in [Section 5.3](#) and [Section 10.4](#).

10.8.5.4. Screen Failures

See [Section 5.4](#).

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

See [Section 5.5](#).

10.8.6. Study Intervention(s) and Concomitant Therapy

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

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

10.8.6.1. Study Intervention(s) Administered

See [Section 6.1](#) for details of BNT162b2.

Additional Intervention Name	Saline Placebo
Type	Placebo
Dose Formulation	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	N/A
Dosage Level(s)	N/A
Route of Administration	Intramuscular injection
Use	Placebo
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

10.8.6.1.1. Administration

Participants will receive 1 dose of study intervention at Visit 201 (Vaccination 1) and Visit 203 (Vaccination 2) in accordance with the substudy's SoA ([Section 10.8.1.3](#)).

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

10.8.6.1.2. Preparation and Dispensing

Study intervention will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way as to ensure that the participants remain blinded.

10.8.6.2. Measures to Minimize Bias: Randomization and Blinding

10.8.6.2.1. Blinding of Site Personnel

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

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the

unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

10.8.6.2.2. Blinding of the Sponsor

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

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.
- An unblinded team supporting interactions with, and analyses for, the DMC (see [Section 10.8.9.4.1](#)). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.

The participant may be unblinded at Visit 205, 1 month after receiving their second study vaccination, to confirm the date of BNT162b2 receipt. The study team will also become unblinded to the participant's original study intervention allocation at this time.

10.8.6.2.3. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

10.8.6.3. Study Intervention Compliance

See [Section 6.4](#).

10.8.6.4. Dose Modification

See [Section 6.5](#).

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

See [Section 6.6](#).

10.8.6.6. Treatment of Overdose

See [Section 6.7](#).

10.8.6.7. Concomitant Therapy

See [Section 6.8](#).

10.8.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See [Section 7](#).

10.8.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 50 mL.

For all participants, other 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 60 consecutive days.

10.8.8.1. Safety Assessments

See [Section 8.2](#).

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

See [Section 8.3](#).

10.8.8.3. Substudy B Procedures

10.8.8.3.1. Visit 201 – Vaccination (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant 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/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Confirm that the participant has received 2 or 3 prior doses of BNT162b2 (30-µg doses) with their last dose at least 4 months (120 days) prior to randomization. Secondary confirmation by another site staff member is required.
- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample (approximately 10 mL) for troponin levels.

- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Explain the e-diary technologies available for this study (see [Section 8.2.4](#)), and assist the participant or his/her parent(s)/legal guardian(s), as appropriate, in downloading the study application onto his or her own device or issue a provisioned device if required.
- Provide instructions on reactogenicity 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.
- 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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - 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.
- 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.
- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.8.8.3.6](#)).

- Ask the participant or his/her parent(s)/legal guardian(s), as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- 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 reactogenicity e-diary to the next visit. Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

10.8.8.3.2. Visit 202 – 4-Day Follow-Up Visit (After Vaccination 1) (2-5 Days After Visit 201)

- Record AEs as described in [Section 8.3](#).
- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 10 mL) for troponin levels.
- Discuss contraceptive use as described in [Section 5.3](#).
- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.8.8.3.6](#)).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- 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 reactogenicity e-diary to the next visit. Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.8.8.3.3. Visit 203 – Vaccination 2 (28 to 35 Days After Visit 201)

- Record AEs as described in [Section 8.3](#).
- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 201 (if any).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

Note: a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. Please see [Section 7.1](#).

- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Collect a blood sample (approximately 10 mL) for troponin levels.
- Unblinded site staff will obtain the participant's study intervention allocation using the IRT system.
- Unblinded site staff will administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure that the participant or his/her parent(s)/legal guardian has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure that the participant or his/her parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.
- Discuss contraceptive use as described in [Section 5.3](#).
- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.8.8.3.6](#)).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- 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 reactogenicity e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

10.8.8.3.4. Visit 204 – 4-Day Follow-Up Visit (After Vaccination 2) (2 to 5 Days After Visit 203)

- Record AEs as described in [Section 8.3](#).
- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 10 mL) for troponin levels.

- Discuss contraceptive use as described in [Section 5.3](#).
- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.8.8.3.6](#)).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- 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 reactogenicity e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.8.8.3.5. Visit 205 – 1-Month Follow-Up Visit (After Vaccination 2) (28-35 Days After Visit 203)

- Record AEs as described in [Section 8.3](#).
- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 203 (if any). Collect a blood sample (approximately 10 mL) for troponin levels.
- Collect the participant's e-diary or assist the participant or his/her parent(s)/legal guardian in removing the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

- The participant may be unblinded at Visit 205, 1 month after receiving their second study vaccination, to confirm the date of BNT162b2 receipt. The study team will also become unblinded to the participant's original study intervention allocation at this time.

10.8.8.3.6. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably 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 (Results from the blood samples collected during the study will be provided to the participant's study physician; however, this will take some time, so the participant should be cautioned not to rely on these results for medical treatment.)

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

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

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

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

If a Grade 3 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever ([Section 8.2.4.4](#)) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever ([Section 8.2.4.4](#)) 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, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

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

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

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

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in [Section 8.2.4.2](#).
- Assess systemic events (if present) in accordance with the grades provided in [Section 8.2.4.3](#).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

10.8.9. Statistical Considerations for Substudy B

See [Section 9](#) for master protocol statistical considerations and substudy specifics below.

10.8.9.1. Statistical Hypotheses

10.8.9.1.1. Estimands

The estimands corresponding to the primary objectives are described in the table in [Section 10.8.3](#).

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

10.8.9.1.2. Statistical Hypotheses

All objectives in this substudy are descriptive. No hypothesis testing is planned.

10.8.9.1.3. Multiplicity Adjustment

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

10.8.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Safety	All participants who receive at least 1 dose of the study intervention.

10.8.9.3. Statistical Analyses

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

10.8.9.3.1. General Considerations

All safety data will be analyzed separately for each age group (12-17, 18-24, and 25-30 years of age) and for all age groups combined.

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	<p>Counts and percentages of participants with elevated troponin I levels before and 4 days and 1 month after administration of BNT162b2 or placebo will be provided for Sequence 1 and Sequence 2 combined. The associated Clopper-Pearson 95% CIs will also be provided (Section 9.3.1.1).</p> <p>The difference in percentages of participants with elevated troponin I levels between BNT162b2 and placebo will be provided at each time point after vaccination (4 days after BNT162b2 minus 4 days after placebo, or 1 month after BNT162b2 minus 1 month after placebo) combining Sequence 1 and Sequence 2. This analysis will be limited to participants with troponin I level measurements at both time points. The</p>

Endpoint	Statistical Analysis Methods
	<p>2-sided 95% CI for the difference in percentages will be calculated using the adjusted Wald interval as described by Agresti and Min (2005)⁴³ for comparing matched proportions. The difference in percentages of participants with elevated troponin I levels between before and after each vaccination (ie, 4 days after BNT162b2 minus before BNT162b2, 4 days after placebo minus before placebo) and associated 95% CI will be summarized in a similar way. Additional assessment based on the crossover design feature may be performed and details will be described in the SAP.</p> <p>In addition, percentages of participants with elevated troponin I levels before and at subsequent time points after each vaccination will be summarized for Sequence 1 and Sequence 2 separately.</p> <p>Descriptive statistics will be provided for each reactogenicity endpoint after each vaccination for Sequence 1 and Sequence 2 separately. 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 (Section 9.3.1.1).</p> <p>Local reactions and systemic events within 7 days after BNT162b2 or placebo administration will also be summarized in a similar way for Sequence 1 and Sequence 2 combined.</p> <p>AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs and SAEs within 1 month after each vaccination will be provided for Sequence 1 and Sequence 2 separately (Section 9.3.1.1).</p> <p>AEs/SAEs will also be summarized within 1 month after BNT162b2 or placebo administration in a similar way for Sequence 1 and Sequence 2 combined.</p>

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

Not applicable.

10.8.9.3.4. Exploratory Endpoint(s)

Not applicable.

10.8.9.4. Interim Analyses

No formal interim analysis will be conducted for this study. Only 1 analysis will be performed at the completion of the study.

10.8.9.4.1. Data Monitoring Committee or Other Independent Oversight Committee

This substudy will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail. The DMC will be responsible for ongoing monitoring of the safety data throughout the study according to the charter.

The recommendations made by the DMC will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, investigators as appropriate.

10.8.9.5. Sample Size Determination

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

Table 8 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes based on anticipated enrollment in each age group and overall. For example, if the true AE rate is 0.10%, with 750 participants in each randomized sequence, there is 53% probability of observing at least 1 AE.

Table 8. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Samples Sizes

Sample Size (N)	Assumed True Event Rate of an AE						
	0.01%	0.02%	0.05%	0.10%	0.50%	1.00%	2.00%
250	0.02	0.05	0.12	0.22	0.71	0.92	>0.99
500	0.05	0.10	0.22	0.39	0.92	>0.99	>0.99
750	0.07	0.14	0.31	0.53	0.98	>0.99	>0.99
1500	0.14	0.26	0.53	0.78	>0.99	>0.99	>0.99

Note: A total of 250 and 500 participants are to be enrolled in each age group within each randomized sequence and overall. A total of 750 and 1500 participants are to be enrolled for all age groups within each randomized sequence and overall.

10.9. Appendix 9: Substudy C**10.9.1. Substudy Summary****10.9.1.1. Synopsis**

See [Section 1.1](#) for a synopsis of Substudy C.

10.9.1.2. Schema

	Visit Number	301	302	303	304
	Visit Description	Booster (Third) Dose of BNT162b2	7 Days After Booster Vaccination	1 Month After Booster Vaccination	6 Months After Booster Vaccination
Participants having received 2 prior doses of 30 µg BNT162b2 at least 5 months (150 days) prior to randomization		BNT162 10-µg OR 30-µg dose			
	Blood draw for immunogenicity	X	X	X	X

10.9.1.3. Schedule of Activities for Substudy C

Visit Number	301	302	303	304
Visit Description	Booster (Third) Dose of BNT162b2	7 Days After Booster Vaccination	1 Month After Booster Vaccination	6 Months After Booster Vaccination
Visit Window	Day 1 ^a	6-8 Days After Visit 301	28 to 35 Days After Visit 301	175-189 Days After Visit 301
Confirm the participant has only received 2 doses of BNT162 at least 5 months (150 days) prior to randomization.	X			
Obtain informed consent/assent	X			
Obtain the participant's prior study and participant number (if applicable)	X			
Assign participant number	X			
Obtain demography and medical history data	X			
Perform clinical assessment ^b	X			
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X
Measure height and weight	X			
Measure temperature (body)	X			
Perform urine pregnancy test (if appropriate)	X			
Confirm use of contraceptives (if appropriate)	X	X	X	
Collect nonstudy vaccine information	X	X	X	
Collect prohibited medication use		X	X	X
Confirm eligibility	X			
Review temporary delay criteria	X			
Collect blood sample for immunogenicity ^c	~10 mL	~10 mL	~10 mL	~10 mL
Obtain randomization number	X			
Obtain study intervention allocation	X			
Administer study intervention	X			
Assess acute reactions for at least 30 minutes after study intervention administration	X			
Explain/review participant communication methods (including for reactogenicity e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X			
Provide/ensure participant has a thermometer and measuring device	X			

Visit Number	301	302	303	304
Visit Description	Booster (Third) Dose of BNT162b2	7 Days After Booster Vaccination	1 Month After Booster Vaccination	6 Months After Booster Vaccination
Visit Window	Day 1 ^a	6-8 Days After Visit 301	28 to 35 Days After Visit 301	175-189 Days After Visit 301
Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following study intervention administration)	X →	X →		
Review ongoing reactogenicity e-diary symptoms with participant and obtain stop dates		X	X	
Request the participant return the e-diary or assist the participant to delete the application			X	
Collect AEs and SAEs as appropriate	X	X	X	X ^d

Abbreviation: HIV = human immunodeficiency virus.

- The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
- Including, if indicated, a physical examination.
- 10 mL is to be collected from participants 12 to 17 years of age.
- Any AEs occurring up to 48 hours after the blood draw must be recorded (see [Section 8.3.1](#)).

10.9.2. Introduction

10.9.2.1. Study Rationale

Substudy C will assess the safety, tolerability, and immunogenicity of a booster (third) dose of BNT162b2 at doses of 10 µg or 30 µg in participants who have completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months (150 days) prior to randomization. The primary immunogenicity objective of the study is to demonstrate that the immune response induced by a booster (third) dose of BNT162b2 at a 10-µg dose is noninferior to the immune response elicited 1 month after the second dose of BNT162b2 at 30 µg (ie, having completed a 2-dose primary series of BNT162b2 [30-µg doses]).

If this objective is successfully met, a lower dose level would allow for greater vaccine accessibility and equity – with more doses being available globally. A more favorable reactogenicity profile may also be demonstrated. Additionally, the results from 306 participants 18 to 55 years of age from the C4591001 study who received a third (booster) dose of 30 µg BNT162b2 a median of 6.8 months after their second dose demonstrated a strong immune response with robust neutralizing antibody titers against the reference strain.²⁰ Immunogenicity of the primary series in participants 12 to 15 of age was shown to be greater than in participants 16 to 25 years of age.²¹ Therefore, the assessment of a 10-µg booster dose in individuals ≥12 years of age who have received the authorized 30-µg 2-dose primary series warrants further investigation. Randomization will be stratified by age with escalation to each higher age group guided by immunogenicity results. This study contains assessments that could be considered standard for a vaccine noninferiority study. Blood samples taken for immunogenicity will establish the level of immune response elicited by each dose level to provide the necessary data to meet the primary endpoint of the study. Immunogenicity will be assessed by SARS-CoV-2 neutralizing titers.

As part of Protocol Amendment 11, progression beyond the 12 through 17 years age group will not occur and no further participants will be enrolled. Active participants at the time of this amendment will also only be followed for 6 months after their last study vaccination. Their final visit will be V304. The rationale for this amendment is that a third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time (hence the potential substrate for enrollment is essentially non-existent) and, for Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine. Both factors contribute to age escalation being operationally unfeasible. Furthermore, since the 30-µg dose level is well tolerated, and in the face of emergence of Omicron and its sublineages for which maximum immune response is desirable, the rationale for a reduced dose level no longer holds.

For participants who have already completed V304 at the time of protocol amendment 11, they will be informed by the investigator site staff of study completion and that no further visits are required.

As part of protocol amendment 12, endpoints and/or analyses that do not pertain to current variant-modified versions of BNT162b2 were removed to expedite remaining testing and to focus on analyses of interest.

See [Section 2.2](#) for the study background.

10.9.2.2. Benefit/Risk Assessment

No additional risks are identified for Substudy C beyond those detailed for the master study (see [Section 2.3](#)).

10.9.2.2.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy C may be:

- Receipt of a booster dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic.
- Receipt of a potentially efficacious booster dose with the potential of reduced reactogenicity.
- Contributing to research to help others in a time of global pandemic.

10.9.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety	Primary Safety	Primary Safety
<ul style="list-style-type: none"> • To evaluate the safety of a booster dose of BNT162b2 when administered at both 10-µg and 30-µg doses 	<p>In participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of participants reporting:</p> <ul style="list-style-type: none"> • Local reactions for up to 7 days following the booster dose • Systemic events for up to 7 days following the booster dose • AEs from the booster dose to 1 month after the booster dose • SAEs from the booster dose to 6 months after the booster dose 	<ul style="list-style-type: none"> • Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity	Primary Immunogenicity	Primary Immunogenicity
<p>To describe the immune response to BNT162b2 10 µg and 30 µg given as the third dose in participants 12 through 17 years of age and a third dose of BNT162b2 30 µg in a randomly selected subset of participants 18 through 55 years of age from study C4591001</p>	<p>In participants complying with the key protocol criteria (evaluable participants) from each vaccine and age group:</p> <p>At baseline (before the third dose) and 1 month after the third dose:</p> <ul style="list-style-type: none"> • GMTs at each time point • GMFRs from baseline (before the third dose) to each subsequent time point after the third dose • Percentage of participants with seroresponse at each time point after the third dose 	<ul style="list-style-type: none"> • SARS-CoV-2 reference-strain–neutralizing titers

Objectives	Estimands	Endpoints
Secondary Immunogenicity	Secondary Immunogenicity	Secondary Immunogenicity
To describe the immune response to BNT162b2 10 µg and 30 µg given as the third dose in participants 12 through 17 years of age ^a	At baseline (before the third dose) and 7 days after the third dose: <ul style="list-style-type: none"> • GMTs at each time point • GMFRs from baseline (before the third dose) to 7 days after the third dose • Percentage of participants with seroresponse at 7 days after the third dose 	<ul style="list-style-type: none"> • SARS-CoV-2 reference-strain–neutralizing titers • SARS-CoV-2 Omicron BA.1–neutralizing titers

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before the study vaccination) for participants in this substudy. If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times \text{LLOQ}$ is considered seroresponse. For the comparator group of participants from study C4591001, seroresponse is defined as achieving a ≥ 4 -fold rise from before Dose 3. If the pre-Dose 3 measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times \text{LLOQ}$ is considered seroresponse.

a. This objective is applicable to the immunogenicity analysis of the first approximately 100 participants performed for DMC review.

10.9.4. Study Design

10.9.4.1. Overall Design

This is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of a booster (third) dose of BNT162b2 at 10 µg or 30 µg. Participants ≥ 12 years of age who have completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months (150 days) prior to randomization will be enrolled. Participants will be randomized at a ratio of 1:1 to receive BNT162b2 at either a 10-µg or 30-µg dose level at Visit 301. Randomization will be stratified by age with escalation to each higher age group guided by immunogenicity results at 7 days after the third dose. A DMC will review safety (e-diary and AE) and immunogenicity data in the first approximately 100 participants with available immunogenicity (~50 participants in each dose level) 7 days after the third dose. Upon confirmation of an acceptable safety and immunogenicity assessment by the DMC, progression of the next age group will occur independently.

As part of protocol amendment 11, progression beyond the 12 through 17 years age group will not occur and no further participants will be enrolled.

Serum blood samples will be collected for immunogenicity at baseline, 7 days after the booster (third) dose, 1 month after the third dose, and 6 months after the third dose. Up to approximately 150 participants will be randomized in the study.

10.9.4.1.1. Scientific Rationale for Substudy C Design

See [Section 1.1](#).

10.9.4.1.2. Diversity of Study Population

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

10.9.4.2. Justification for Dose

See [Section 4.3](#) for a justification of the 30-µg BNT162b2 dose used in Substudy C.

If a booster (third) dose of BNT162b2 at 10 µg induces an immune response that is noninferior to the immune responses elicited 1 month after the second dose of BNT162b2 at 30 µg (ie, following completion of a 2-dose primary series of BNT162b2 [30-µg doses]), this finding could have significant implications on vaccine accessibility and equity globally, as it would allow for the availability of more doses.

10.9.4.3. End of Study Definition

See [Section 4.4](#).

10.9.5. Study Population

Details of the master and Substudy C eligibility criteria are shown in [Section 5](#). Participants must meet all of the general inclusion and exclusion criteria as specified for both the master protocol and Substudy C–specific inclusion and exclusion criteria.

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. Male or female participants ≥ 12 years of age, inclusive, who have received 2 prior doses of 30 µg BNT162b2 19 to 60 days apart, with the second dose being at least 150 days before Visit 301 (Day 1)

Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

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

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in [Section 10.15](#).

Informed Consent:

4. Capable of giving personal signed informed consent/assent, have parent(s)/legal guardian capable of giving signed informed consent as described in [Appendix 1](#), 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/electronically signed informed consent (and assent) from each study participant's legal guardian (as defined in [Appendix 1](#), and the participant's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

10.9.5.2. Exclusion Criteria

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

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
3. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.
4. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
5. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥ 14 days at a dose of ≥ 20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. Prior receipt of any COVID-19 vaccine other than BNT162b2.

Other Exclusions:

10. Investigator site staff or Pfizer-BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
11. Receipt of medications intended to prevent COVID-19.
12. Prior receipt of more than 2 doses of BNT162b2 30 μ g.
13. Participation in other studies involving study intervention within 28 days prior to study entry through and including 28 days after the last dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

10.9.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy C as detailed in [Section 5.3](#) and [Section 10.4](#).

10.9.5.4. Screen Failures

See [Section 5.4](#).

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

See [Section 5.5](#).

10.9.6. Study Intervention(s) and Concomitant Therapy

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

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S):
10 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S):
30 µg

10.9.6.1. Study Intervention(s) Administered

See [Section 6.1](#) for details of BNT162b2.

10.9.6.1.1. Administration

Participants will receive 1 dose of study intervention at Visit 301 (booster [third] dose of BNT162b2) in accordance with the substudy's SoA ([Section 10.9.1.3](#)).

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

10.9.6.1.2. Preparation and Dispensing

Study intervention will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way as to ensure that the participants remain blinded.

10.9.6.2. Measures to Minimize Bias: Randomization and Blinding

10.9.6.2.1. Blinding of Site Personnel

In this observer-blinded substudy, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

10.9.6.2.2. Blinding of the Sponsor

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

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.
- An unblinded team supporting interactions with, and analyses for, the DMC (see [Section 10.9.9.4.2](#)). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.
- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.

The participant may be unblinded to confirm the dose of BNT162b2 received 3 months after receiving their study vaccination. The study team will also become unblinded to the participant's original study intervention allocation at this time.

10.9.6.2.3. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

10.9.6.3. Study Intervention Compliance

See [Section 6.4](#).

10.9.6.4. Dose Modification

See [Section 6.5](#).

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

See [Section 6.6](#).

10.9.6.6. Treatment of Overdose

See [Section 6.7](#).

10.9.6.7. Concomitant Therapy

See [Section 6.8](#).

10.9.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See [Section 7](#).

10.9.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 40 mL.

For all participants, other 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 60 consecutive days.

10.9.8.1. Efficacy and/or Immunogenicity Assessments for Substudy C

10.9.8.1.1. Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the [SoA](#). The test to be performed will be the SARS-CoV-2 neutralizing assay. Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory.

10.9.8.2. Safety Assessments

See [Section 8.2](#).

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

See [Section 8.3](#).

10.9.8.4. Substudy C Procedures

10.9.8.4.1. Visit 301 – Booster (Third) Dose of BNT162b2 (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/participant's parent(s)/legal guardian(s). 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. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Confirm the participant has only received 2 doses of BNT162b2 at least 5 months (150 days) prior to randomization. Secondary confirmation by another site staff member is required.
- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity.
- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Explain the e-diary technologies available for this study (see [Section 8.2.4](#)), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto his or her own device or issue a provisioned device if required.
- Provide instructions on reactogenicity 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.
- 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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - 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.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.9.8.5](#)).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- 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 and an unblinded dispenser/administrator updates the study intervention accountability records.

10.9.8.4.2. Visit 302 – 7 Days After Booster Vaccination (6-8 Days After Visit 301)

- Record AEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- Collect a blood sample for immunogenicity.
- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Discuss contraceptive use as described in [Section 5.3](#).
- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.9.8.5](#)).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- 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.

10.9.8.4.3. Visit 303 – 1 Month After Booster Vaccination (28 to 35 Days After Visit 301)

- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 301 (if any).
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity.
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Collect the participant's reactogenicity e-diary or assist the participant or his/her parent(s)/legal guardian to remove the study application from his or her own personal device.
- Discuss contraceptive use as described in [Section 5.3](#).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- 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 and an unblinded dispenser/administrator updates the study intervention accountability records.

10.9.8.4.4. Visit 304 – 6 Months After Booster Vaccination (175 to 189 Days After Visit 301)

For participants who have already completed V304 at the time of protocol amendment 11, they will be informed by the investigator site staff of study completion and that no further visits are required.

- Record AEs as described in [Section 8.3](#).

- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 303 (if any).
- Collect a blood sample for immunogenicity.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.9.8.5. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably 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.

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

If a Grade 3 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever ([Section 8.2.4.4](#)) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever ([Section 8.2.4.4](#)) 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, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

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

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

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

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in [Section 8.2.4.2](#).
- Assess systemic events (if present) in accordance with the grades provided in [Section 8.2.4.3](#).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

10.9.9. Statistical Considerations for Substudy C

See [Section 9](#) for master protocol statistical considerations and substudy specifics below.

10.9.9.1. Statistical Hypotheses

10.9.9.1.1. Estimands

The estimands corresponding to the primary and secondary objectives are described in the table in [Section 10.9.3](#).

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

10.9.9.1.2. Statistical Hypotheses

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

10.9.9.1.3. 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, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized participants who receive the study vaccine to which they are randomized, have a 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 randomized participants who receive at least 1 dose of the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive at least 1 dose of the study intervention.

10.9.9.3. Statistical Analyses

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

10.9.9.3.1. General Considerations

Refer to [Section 9.3.1](#) for general considerations of statistical analyses.

In this substudy, all safety and immunogenicity data will be analyzed separately for each age group.

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

Endpoint	Statistical Analysis Methods
Safety	<ul style="list-style-type: none"> Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group in each age group. Local reactions and systemic events from Day 1 through Day 7 after the third dose (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after the third dose will be provided for each vaccine group within each age group.
Immunogenicity	<p>GMTs and GMFRs of SARS-CoV-2 reference-strain–neutralizing titers</p> <p>Percentage of participants with seroresponse to the reference strain</p> <ul style="list-style-type: none"> GMTs at baseline (before the third dose) and 1 month after vaccination and GMFRs of SARS-CoV-2 reference-strain–neutralizing titers from baseline (before the third dose) to 1 month after vaccination, along with the associated 2-sided 95% CIs, will be provided for each age and vaccine group using the statistical method described in Section 9.3.1.2.1 and Section 9.3.1.2.2. The percentages of participants with seroresponse to the reference strain at 1 month after the third dose, and the associated Clopper-Pearson 95% CIs, will be provided for each age and vaccine group. The analyses will be performed in participants without evidence of SARS-CoV-2 infection, and in participants with and without evidence of SARS-CoV-2 infection.

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

Endpoint	Statistical Analysis Methods
Immunogenicity	<p>GMTs and GMFRs of SARS-CoV-2 reference-strain– and Omicron BA.1–neutralizing titers</p> <p>Percentage of participants with seroresponse to the reference strain and Omicron BA.1</p> <ul style="list-style-type: none">• GMTs and GMFRs of SARS-CoV-2 reference strain and Omicron BA.1–neutralizing titers from baseline (before the third dose) to 7 days after vaccination, and percentage of participants with seroresponse to reference strain and Omicron BA.1 at 7 days after vaccination, along with the associated 2-sided 95% CIs, will be provided using the same statistical methods as described above for the primary endpoint.

10.9.9.3.4. Exploratory Endpoint(s) Analysis

Not applicable.

10.9.9.4. Interim Analyses

An administrative interim analysis is planned for each of the following age groups: 12 through 17 years, 18 through 30 years, and 31 through 55 years, when 7-day post–booster dose immunogenicity data are available from approximately the first 100 participants (~50 participants in each booster dose–level group). The purpose of the administrative interim analysis is to inform initiation of enrollment for the next age group. The analysis will be performed by an unblinded DMC reporting team. Only group-level unblinded results will be shared with limited sponsor personnel.

The administrative interim analysis of the first 100 participants in the 12 through 17 years age group was completed. The DMC did not raise any concerns for age escalation; however, as part of protocol amendment 11, progression beyond the 12 through 17 years age group will not occur and no further participants will be enrolled. The rationale for this amendment is that a third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time (hence the potential substrate for enrollment is essentially nonexistent) and, for Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine. Both factors contribute to age escalation being operationally unfeasible. Furthermore, since the 30-μg dose level is well tolerated, and in the face of emergence of Omicron and its sublineages for which maximum immune response is desirable, the rationale for a reduced dose level no longer holds.

Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below.

10.9.9.4.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Safety data through 1 month after the third dose in each dose level group.
- Immunogenicity data through 1 month after the third dose for participants enrolled in this study and for the comparator group from the C4591001 study.
- Complete safety analysis approximately 6 months after the third dose in each dose group.

Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses conducted while the study is ongoing will be performed by an unblinded team.

10.9.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize a DMC that will be used to review safety data (e-diary and AE) and immunogenicity in the first approximately 100 participants with available immunogenicity data (~50 participants in each dose level of BNT162b2) 7 days after the third dose. Upon confirmation of an acceptable safety and immunogenicity assessment by the DMC, progression of each age group will occur independently.

The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail. The DMC will be responsible for ongoing monitoring of the safety data throughout the study according to the charter.

The recommendations made by the DMC will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, investigators as appropriate.

10.9.9.5. Sample Size Determination

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

For safety outcomes, [Table 9](#) shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 1%, with 75 participants in a vaccine group, there is 53% probability of observing at least 1 AE.

**Table 9. Probability of Observing at 1 Least AE by Assumed True Event Rates
With Different Sample Sizes**

Assumed True Event Rate of an AE	N=50	N=75	N=150
0.01%	0	0.01	0.01
0.02%	0.01	0.01	0.03
0.04%	0.02	0.03	0.06
0.06%	0.03	0.04	0.09
0.08%	0.04	0.06	0.11
0.10%	0.05	0.07	0.14
0.15%	0.07	0.11	0.2
0.20%	0.1	0.14	0.26
0.25%	0.12	0.17	0.31
0.30%	0.14	0.2	0.36
0.50%	0.22	0.31	0.53
1%	0.39	0.53	0.78
2%	0.64	0.78	0.95
3%	0.78	0.9	0.99
5%	0.92	0.98	>0.99
10%	0.99	>0.99	>0.99

10.10. Appendix 10: Substudy D

10.10.1. Substudy Summary

10.10.1.1. Synopsis

See [Section 1.1](#) for a synopsis of Substudy D.

10.10.1.2. Schema

10.10.1.2.1. Participants in Cohort 1

Cohort	Visit Number	401	402	403	404	405
	Visit Description	SSD Vaccination 1	1-Month Follow-Up Visit and SSD 2 nd Vaccination	1-Month Follow-Up Visit after SSD 2 nd Vaccination ^a	3-Month Follow-Up Visit After Last SSD Vaccination	6-Month Follow-Up Visit After Last SSD Vaccination
Cohort 1: Participants 18-55 years of age having received 2 doses of BNT162b2 before enrollment (3-8 months after last dose)	Group 1: (N=205)	BNT162b2 OMI 30-µg dose				
	Group 2: (N=205)	BNT162b2 OMI 30-µg dose	BNT162b2 OMI 30-µg dose			
	Group 2b: (N=205)	BNT162b2 30-µg dose				
	Blood draw for immunogenicity	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL
	Collect blood sample for PBMC isolation ^b	~120 mL	~120 mL	~120 mL	~120 mL	

Abbreviations: HLA = human leukocyte antigen; PBMC = peripheral blood mononuclear cell; SSD = Substudy D.

- a. Only for those participants randomized to receive a second dose of BNT162b2 OMI as part of Substudy D.
- b. Additional 120 mL for PBMC isolation (and 5 mL for HLA typing at Visit 401) for select participants at select sites only. See [Section 10.10.8.2](#)

10.10.1.2.2. Participants in Cohort 2

Cohort	Visit Number	401	402	404	404a	404b	404c	405
	Visit Description	SSD Vaccination 1	1-Month Follow-Up Visit	3-Month Follow-Up Visit and 2 nd SSD Vaccination	7-Day Follow-Up Visit After 2 nd SSD Vaccination ^a	1-Month Follow-Up Visit After 2 nd SSD Vaccination ^a	3-Month Follow-Up Visit After 2 nd SSD Vaccination ^a	6-Month Follow-Up Visit After Last SSD Vaccination
Cohort 2: Participants 18-55 years of age having received 3 doses of BNT162b2 before enrollment (3-6 months after last dose)	Group 3: (N=300)	BNT162b2 OMI 30-µg dose		BNT162b2 OMI 30-µg dose				
	Group 4: (N=300)	BNT162b2 30-µg dose		BNT162b2 OMI 30-µg dose				
	Blood draw for immunogenicity	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL
	Collect blood sample for PBMC isolation ^b	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	

Abbreviations: HLA = human leukocyte antigen; PBMC = peripheral blood mononuclear cell; SSD = Substudy D.

- Only for those participants who consent to receive a dose of BNT162b2 OMI at Visit 404 as part of Substudy D.
- Additional 120 mL for PBMC isolation (and 5 mL for HLA typing at Visit 401) for select participants at select sites only. See [Section 10.10.8.2](#).

10.10.1.2.3. Participants in Cohort 3

	Visit Number	501	502	503	504	505	506	507	508
	Visit Description	Vaccination 1	Vaccination 2 3 Weeks After Vaccination 1	1-Week Follow-Up Visit After Vaccination 2 ^a	1-Month Follow-Up Visit After Vaccination 2	3-Month Follow-Up Visit After Vaccination 2	6-Month Follow-Up Visit After Vaccination 2 and Administration of Vaccination 3 ^b	1-Month Follow-Up Visit After Vaccination 3	6-Month Follow-Up Visit After Vaccination 3
Cohort 3: COVID-19 vaccine- naïve participants 18-55 years of age	Group 5: (N=205)	BNT162b2 OMI 30-µg dose	BNT162b2 OMI 30-µg dose				BNT162b2 30-µg dose		
	Blood draw for immunogenicity	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL
	Collect blood sample for PBMC isolation ^c	~120 mL		~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL

Abbreviations: HLA = human leukocyte antigen; PBMC = peripheral blood mononuclear cell.

- Only for those participants who are part of the group for description of cell-mediated immune response.
- Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.
- Additional 120 mL for PBMC isolation (and 5 mL for HLA typing at Visit 501) for select participants at select sites only. See [Section 10.10.8.2](#).

10.10.1.3. Schedule of Activities for Substudy D

10.10.1.3.1. Cohort 1

Visit Number	401	402	403	404	405	Unplanned
Visit Description	SSD Vaccination 1 ^a	1-Month Follow-Up Visit After SSD Vax 1 and SSD Vax 2 ^b	1-Month Follow-Up Visit After SSD Vax 2 ^b	3-Month Follow-Up Visit After Last SSD Vaccination	6-Month Follow-Up Visit After Last SSD Vaccination	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1	28 to 35 Days After Visit 401	28 to 35 Days After Visit 402	85 to 95 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)	175 to 189 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)	Optimally Within 3 Days After Potential COVID-19 Illness Onset
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2			
Obtain informed consent	X					
Obtain the participant's prior study and participant number (if applicable)	X					
Confirm participant's past BNT162b2 experience (3-8 months since the last dose)	X					
Obtain demography and medical history data	X					
Perform clinical assessment ^d	X					
Measure height and weight	X					
Measure temperature (body)	X	X ^b				
Perform urine pregnancy test (if appropriate)	X	X ^b				

Visit Number	401	402	403	404	405	Unplanned
Visit Description	SSD Vaccination 1 ^a	1-Month Follow-Up Visit After SSD Vax 1 and SSD Vax 2 ^b	1-Month Follow-Up Visit After SSD Vax 2 ^b	3-Month Follow-Up Visit After Last SSD Vaccination	6-Month Follow-Up Visit After Last SSD Vaccination	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1	28 to 35 Days After Visit 401	28 to 35 Days After Visit 402	85 to 95 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)	175 to 189 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)	Optimally Within 3 Days After Potential COVID-19 Illness Onset
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2			
Confirm use of contraceptives (if appropriate)	X	X	X			
Collect prohibited medication use		X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X	
For participants who are HIV-positive, record the latest CD4 count and HIV viral load	X	X		X	X	
Confirm eligibility	X	X ^b				
Review temporary delay criteria	X	X ^b				
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation ^e	~120 mL	~120 mL	~120 mL	~120 mL		
Collect blood sample for HLA typing ^e	~5 mL					

Visit Number	401	402	403	404	405	Unplanned
Visit Description	SSD Vaccination 1 ^a	1-Month Follow-Up Visit After SSD Vax 1 and SSD Vax 2 ^b	1-Month Follow-Up Visit After SSD Vax 2 ^b	3-Month Follow-Up Visit After Last SSD Vaccination	6-Month Follow-Up Visit After Last SSD Vaccination	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1	28 to 35 Days After Visit 401	28 to 35 Days After Visit 402	85 to 95 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)	175 to 189 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)	Optimally Within 3 Days After Potential COVID-19 Illness Onset
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2			
Obtain nasal (midturbinate) swab(s)	X	X ^b				X
Obtain randomization number and study intervention allocation using the IRT system	X					
Administer study intervention	X	X ^b				
Assess acute reactions for at least 30 minutes after study intervention administration	X	X ^b				
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X	X				

Visit Number	401	402	403	404	405	Unplanned
Visit Description	SSD Vaccination 1 ^a	1-Month Follow-Up Visit After SSD Vax 1 and SSD Vax 2 ^b	1-Month Follow-Up Visit After SSD Vax 2 ^b	3-Month Follow-Up Visit After Last SSD Vaccination	6-Month Follow-Up Visit After Last SSD Vaccination	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1	28 to 35 Days After Visit 401	28 to 35 Days After Visit 402	85 to 95 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)	175 to 189 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)	Optimally Within 3 Days After Potential COVID-19 Illness Onset
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2			
Provide/ensure the participant has a thermometer and measuring device	X	X ^b				
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←→	←→				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X			
Collect AEs and SAEs as appropriate	X	X	X	X ^f	X ^f	X ^f
Collect e-diary or assist the participant to delete application					X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X

Visit Number	401	402	403	404	405	Unplanned
Visit Description	SSD Vaccination 1 ^a	1-Month Follow-Up Visit After SSD Vax 1 and SSD Vax 2 ^b	1-Month Follow-Up Visit After SSD Vax 2 ^b	3-Month Follow-Up Visit After Last SSD Vaccination	6-Month Follow-Up Visit After Last SSD Vaccination	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1	28 to 35 Days After Visit 401	28 to 35 Days After Visit 402	85 to 95 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)	175 to 189 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)	Optimally Within 3 Days After Potential COVID-19 Illness Onset
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2			
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs	X	X	X	X		

Abbreviations: HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; SSD = Substudy D.

- The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
- Only for those participants randomized to receive a second dose of BNT162b2 OMI as part of Substudy D.
- The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
- Including, if indicated, a physical examination.
- Additional 120 mL for PBMC isolation and 5 mL for HLA typing for select participants at select sites only.
- Any AEs occurring up to 48 hours after the blood draw must be recorded (see [Section 8.3.1](#)).

10.10.1.3.2. Cohort 2

Visit Number	401	402	404	404a	404b	404c	405	Unplanned
Visit Description	SSD Vaccination 1 ^a	1-Month Follow-Up Visit After SSD Vax 1	3-Month Follow-Up Visit and 2 nd SSD Vaccination ^b	7-Day Follow-Up Visit After SSD Vax 2 ^b	1-Month Follow-Up Visit After SSD Vax 2 ^b	3-Month Follow-Up Visit After SSD Vax 2 ^b	6-Month Follow-Up Visit After Last SSD Vaccination	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1	28 to 35 Days After Visit 401	85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2 ^d	5 to 9 Days After Visit 404	28 to 35 Days After Visit 404	85 to 95 Days After Visit 404	175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)	Optimally Within 3 Days After Potential COVID-19 Illness Onset
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2					
Obtain informed consent	X		X ^b					
Obtain the participant's prior study and participant number (if applicable)	X							
Confirm participant's past BNT162b2 experience (3-8 months since the last dose)	X							
Obtain demography and medical history data	X							
Perform clinical assessment ^c	X							
Measure height and weight	X							
Measure temperature (body)	X		X ^b					
Perform urine pregnancy test (if appropriate)	X		X ^b					

Visit Number	401	402	404	404a	404b	404c	405	Unplanned
Visit Description	SSD Vaccination 1 ^a	1-Month Follow-Up Visit After SSD Vax 1	3-Month Follow-Up Visit and 2 nd SSD Vaccination ^b	7-Day Follow-Up Visit After SSD Vax 2 ^b	1-Month Follow-Up Visit After SSD Vax 2 ^b	3-Month Follow-Up Visit After SSD Vax 2 ^b	6-Month Follow-Up Visit After Last SSD Vaccination	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1	28 to 35 Days After Visit 401	85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2 ^d	5 to 9 Days After Visit 404	28 to 35 Days After Visit 404	85 to 95 Days After Visit 404	175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)	Optimally Within 3 Days After Potential COVID-19 Illness Onset
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2					
Confirm use of contraceptives (if appropriate)	X	X	X ^b	X	X			
Collect prohibited medication use		X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X	X	X	
For participants who are HIV-positive, record the latest CD4 count and HIV viral load	X	X	X		X	X	X	
Confirm eligibility	X		X ^b					
Review temporary delay criteria	X		X ^b					
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation ^f	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL		
Collect blood sample for HLA typing ^f	~5 mL							
Obtain nasal (midturbinate) swab(s)	X		X ^b					X

Visit Number	401	402	404	404a	404b	404c	405	Unplanned
Visit Description	SSD Vaccination 1 ^a	1-Month Follow-Up Visit After SSD Vax 1	3-Month Follow-Up Visit and 2 nd SSD Vaccination ^b	7-Day Follow-Up Visit After SSD Vax 2 ^b	1-Month Follow-Up Visit After SSD Vax 2 ^b	3-Month Follow-Up Visit After SSD Vax 2 ^b	6-Month Follow-Up Visit After Last SSD Vaccination	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1	28 to 35 Days After Visit 401	85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2 ^d	5 to 9 Days After Visit 404	28 to 35 Days After Visit 404	85 to 95 Days After Visit 404	175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)	Optimally Within 3 Days After Potential COVID-19 Illness Onset
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2					
Obtain randomization number and study intervention allocation using the IRT system	X							
Administer study intervention	X		X ^b					
Assess acute reactions for at least 30 minutes after study intervention administration	X		X ^b					
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X		X ^b					
Provide/ensure the participant has a thermometer and measuring device	X		X ^b					

Visit Number	401	402	404	404a	404b	404c	405	Unplanned
Visit Description	SSD Vaccination 1 ^a	1-Month Follow-Up Visit After SSD Vax 1	3-Month Follow-Up Visit and 2 nd SSD Vaccination ^b	7-Day Follow-Up Visit After SSD Vax 2 ^b	1-Month Follow-Up Visit After SSD Vax 2 ^b	3-Month Follow-Up Visit After SSD Vax 2 ^b	6-Month Follow-Up Visit After Last SSD Vaccination	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1	28 to 35 Days After Visit 401	85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2 ^d	5 to 9 Days After Visit 404	28 to 35 Days After Visit 404	85 to 95 Days After Visit 404	175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)	Optimally Within 3 Days After Potential COVID-19 Illness Onset
				ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2				
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←→		←→					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X	X			
Collect AEs and SAEs as appropriate	X	X	X ^g	X	X	X ^g	X ^g	X
Collect e-diary or assist the participant to delete application							X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X

Visit Number	401	402	404	404a	404b	404c	405	Unplanned
Visit Description	SSD Vaccination 1 ^a	1-Month Follow-Up Visit After SSD Vax 1	3-Month Follow-Up Visit and 2 nd SSD Vaccination ^b	7-Day Follow-Up Visit After SSD Vax 2 ^b	1-Month Follow-Up Visit After SSD Vax 2 ^b	3-Month Follow-Up Visit After SSD Vax 2 ^b	6-Month Follow-Up Visit After Last SSD Vaccination	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1	28 to 35 Days After Visit 401	85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2 ^d	5 to 9 Days After Visit 404	28 to 35 Days After Visit 404	85 to 95 Days After Visit 404	175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)	Optimally Within 3 Days After Potential COVID-19 Illness Onset
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2					
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs	X	X	X	X	X	X		

Abbreviations: HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; SSD = Substudy D.

- The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
- Only for those participants who consent to receive a dose of BNT162b2 OMI at Visit 404 as part of Substudy D.
- The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
- For those participants who consent to receive a second dose of BNT162b2 OMI as part of Substudy D, the Visit 3 window is 85 to 123 days.
- Including, if indicated, a physical examination.
- Additional 120 mL for PBMC isolation and 5 mL for HLA typing for select participants at select sites only.
- Any AEs occurring up to 48 hours after the blood draw must be recorded (see [Section 8.3.1](#)).

10.10.1.3.3. Cohort 3

Visit Number	501	502	503	504	505	506	507	508	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Week Follow-Up Visit After Vaccination 2 ^a	1-Month Follow-Up Visit After Vaccination 2	3-Month Follow-Up Visit After Vaccination 2	6-Month Follow-Up Visit After Vaccination 2 and Administration of Vaccination 3 ^b	1-Month Follow-Up Visit After Vaccination 3	6-Month Follow-Up Visit After Vaccination 3	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1 ^d	19 to 23 Days After Visit 501	6 to 8 Days After Visit 502	28 to 35 Days After Visit 502	85 to 95 Days After Visit 502	150 to 199 Days After Visit 502	28 to 35 Days After Visit 506	175 to 189 Days After Visit 506	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Obtain informed consent	X								
Assign participant number	X								
Obtain demography and medical history data	X								
Perform clinical assessment ^e	X								
Measure height and weight	X								
Measure temperature (body)	X	X				X			
Perform urine pregnancy test (if appropriate)	X	X				X			
Confirm use of contraceptives (if appropriate)	X	X	X	X		X	X		
Collect nonstudy vaccine information	X	X	X	X	X	X	X		
Collect prohibited medication use		X	X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X			X	X	X	X	X	
Confirm eligibility	X	X				X			
Review temporary delay criteria	X	X				X			
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation ^f	~120 mL		~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	
Collect blood sample for HLA typing ^f	~5 mL								

Visit Number	501	502	503	504	505	506	507	508	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Week Follow-Up Visit After Vaccination 2 ^a	1-Month Follow-Up Visit After Vaccination 2	3-Month Follow-Up Visit After Vaccination 2	6-Month Follow-Up Visit After Vaccination 2 and Administration of Vaccination 3 ^b	1-Month Follow-Up Visit After Vaccination 3	6-Month Follow-Up Visit After Vaccination 3	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1 ^d	19 to 23 Days After Visit 501	6 to 8 Days After Visit 502	28 to 35 Days After Visit 502	85 to 95 Days After Visit 502	150 to 199 Days After Visit 502	28 to 35 Days After Visit 506	175 to 189 Days After Visit 506	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Obtain nasal (midturbinate) swab	X	X				X			X
Obtain the participant's vaccine vial allocation using the IRT system	X	X				X			
Administer study intervention	X	X				X ^b			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X				X			
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X	X				X			
Provide/ensure the participant has a thermometer and measuring device	X	X				X			
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	↔	↔				↔			
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X			X		
Collect AEs and SAEs as appropriate	X	X	X	X	X ^g	X	X	X ^g	X
Collect e-diary or assist the participant to delete application								X	

Visit Number	501	502	503	504	505	506	507	508	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Week Follow-Up Visit After Vaccination 2 ^a	1-Month Follow-Up Visit After Vaccination 2	3-Month Follow-Up Visit After Vaccination 2	6-Month Follow-Up Visit After Vaccination 2 and Administration of Vaccination 3 ^b	1-Month Follow-Up Visit After Vaccination 3	6-Month Follow-Up Visit After Vaccination 3	Potential COVID-19 Illness Visit ^c
Visit Window (Days)	Day 1 ^d	19 to 23 Days After Visit 501	6 to 8 Days After Visit 502	28 to 35 Days After Visit 502	85 to 95 Days After Visit 502	150 to 199 Days After Visit 502	28 to 35 Days After Visit 506	175 to 189 Days After Visit 506	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)									X
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs	X	X	X	X	X	X	X		

Abbreviations: HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell.

- Only for those participants who are part of the group for description of cell-mediated immune response.
- Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.
- The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
- The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
- Including, if indicated, a physical examination.
- Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants at select sites only.
- Any AEs occurring up to 48 hours after the blood draw must be recorded (see [Section 8.3.1](#)).

10.10.2. Introduction

10.10.2.1. Study Rationale

On 24 November 2021, South Africa reported the identification of a new SARS-CoV-2 variant, B.1.1.529, to the WHO. On 26 November 2021 and 30 November 2021, the WHO and the US, respectively, classified this new variant as a VOC and named it Omicron. The Omicron variant has also been detected in several European countries, as well as in North/South America, Asia, and Australia.⁴⁴

The Omicron variant has many concerning spike protein mutations, some of which are known from other variants to be associated with reduced neutralization by convalescent and vaccine sera. Specific characteristics unique to Omicron are that the spike protein is characterized by at least 30 amino acid substitutions, 3 small deletions, and 1 small insertion. Notably, 15 of the 30 amino acid substitutions are in the receptor-binding domain. There are also a number of changes and deletions in other genomic regions.²³

In regard to transmissibility, it is currently unknown how efficiently Omicron can spread from person to person. The replacement of Delta by Omicron as the predominant variant in South Africa raises concerns that it may be more transmissible than Delta, but because of the low number of cases in South Africa when it emerged, it is unclear if this variant is more transmissible than the Delta variant. Analysis of the changes in the spike protein indicate that Omicron is likely to have increased transmission compared to the original SARS-CoV-2 virus, but it is difficult to infer if it is more transmissible than Delta. In addition, it is unclear if infection with Omicron is associated with more severe disease. Lastly, to date there are no published data available to assess the ability of sera from vaccinated persons or those with previous SARS-CoV-2 infection to neutralize the Omicron variant.²³ Laboratory and epidemiological studies are needed to assess the impact of the Omicron variant on vaccine effectiveness and breakthrough infections, including in individuals who have received booster doses.²³

Pfizer has developed a new vaccine, BNT162b2 OMICRON (B.1.1.529), which is a BNT162b2 RNA-LNP vaccine utilizing modified RNA and encoding the P2 S containing Omicron B.1.1.529 variant-specific mutations. This new vaccine will be utilized in Substudy D. Substudy D has been designed to assess the safety, tolerability, and immunogenicity of BNT162b2 OMI within 3 different cohorts: 1) participants who have previously received 2 doses of BNT162b2 and will receive either 1 dose of BNT162b2 or 1 or 2 doses of BNT162b2 OMI; 2) participants who have previously received 3 doses of BNT162b2 and will receive a fourth dose of either BNT162b2 or BNT162b2 OMI (participants will be offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up); and 3) participants who are BNT162b2-naïve and will receive 2 doses of BNT162b2 OMI, followed by a dose of BNT162b2.

As part of protocol amendment 11, active participants in Cohort 1 and Cohort 2 at the time of this amendment will only be followed for 6 months after their last study vaccination, which aligns with the protocol-specified safety reporting period. As of Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine, and therefore it is unnecessary to prolong the participation of individuals in the study and take immunogenicity samples 12 months after vaccination for the monovalent Omicron vaccine. Their final visit will be V405.

For participants who have already completed V405 at the time of protocol amendment 11, they will be informed by the investigator site staff of study completion and that no further visits are required.

As part of protocol amendment 12, endpoints and/or analyses that do not pertain to current variant-modified versions of BNT162b2 were removed to expedite remaining testing and to focus on analyses of interest.

See [Section 2.2](#) for the study background.

10.10.2.2. Benefit/Risk Assessment

No additional risks are identified for Substudy D beyond those detailed for the master study (see [Section 2.3](#)).

10.10.2.2.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy D may be:

- Receipt of a third, fourth, or fifth dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic.
- Contributing to research to help others in a time of global pandemic.

10.10.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety		
<ul style="list-style-type: none"> To describe the safety and tolerability profile of BNT162b2 OMI given as the third, fourth, or fifth dose to BNT162b2-experienced participants, or as a 2-dose series to COVID-19 vaccine-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third or fourth dose to BNT162b2-experienced participants (Group 2b, Group 4, and Group 5) 	<p>In participants receiving at least 1 dose of study intervention, the percentage of participants reporting:</p> <ul style="list-style-type: none"> Local reactions for up to 7 days following each dose Systemic events for up to 7 days following each dose AEs from the first study vaccination (received in this study) through 1 month after the last study vaccination SAEs from the first study vaccination (received in this study) through 6 months after the last study vaccination 	<ul style="list-style-type: none"> Local reactions (pain at the injection site, redness, and swelling) Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) AEs SAEs
Primary Immunogenicity <i>BNT162b2-experienced participants</i>		
G1vG2bA: To descriptively compare the anti-Omicron immune response after 1 dose of BNT162b2 OMI to after 1 dose of BNT162b2 given as the third dose in BNT162b2-experienced participants	<p>In participants complying with the key protocol criteria (evaluable participants) and with evidence of past SARS-CoV-2 infection:</p> <ul style="list-style-type: none"> GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI to those at 1 month after 1 dose of BNT162b2 given as the third dose in BNT162b2-experienced participants The difference in percentages of participants with seroresponse^a to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI and at 1 month after 1 dose of BNT162b2 given as the third dose in BNT162b2-experienced participants 	SARS-CoV-2 Omicron-neutralizing titers
G2vG2bA: To descriptively compare the anti-Omicron immune response after 2 doses of BNT162b2 OMI given as the third and fourth dose to after 1 dose of BNT162b2 given as the third dose in BNT162b2-experienced participants	<p>In participants complying with the key protocol criteria (evaluable participants) and with evidence of past SARS-CoV-2 infection:</p> <ul style="list-style-type: none"> GMR of the Omicron-neutralizing titers at 1 month after 2 doses of BNT162b2 OMI to those at 1 month after 1 dose of BNT162b2 given as the third (and fourth) dose in BNT162b2-experienced participants The difference in percentages of participants with seroresponse^a to the Omicron strain at 1 month after 2 doses of BNT162b2 OMI and at 1 month after 1 dose of BNT162b2 given as the third (and fourth) dose in BNT162b2-experienced participants 	SARS-CoV-2 Omicron-neutralizing titers

Objectives	Estimands	Endpoints
G3vG4A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention) of past SARS-CoV-2 infection: <ul style="list-style-type: none"> GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI to those at 1 month after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants The difference in percentages of participants with seroresponse^a to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI and at 1 month after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants 	SARS-CoV-2 Omicron-neutralizing titers
COVID-19 vaccine-naïve participants		
G5A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response after 2 doses of BNT162b2 OMI compared to after 2 doses of BNT162b2 in participants ^b selected from the C4591001 study	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2 OMI or BNT162b2 as appropriate) of past SARS-CoV-2 infection: <ul style="list-style-type: none"> GMR of the Omicron-neutralizing titers 1 month after the second dose of BNT162b2 OMI to 1 month after the second dose of BNT162b2 in participants selected from the C4591001 study The difference in percentages of participants with seroresponse^a to the Omicron strain at 1 month after the second dose of BNT162b2 OMI and at 1 month after the second dose of BNT162b2 in participants selected from the C4591001 study 	SARS-CoV-2 Omicron-neutralizing titers
Secondary Immunogenicity BNT162b2-experienced participants		
G3vG4B: To demonstrate the “super” superiority of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants	Same as GMR estimand of G3vG4A	Same as G3vG4A

Objectives	Estimands	Endpoints
COVID-19 vaccine-naïve participants		
G5B: To demonstrate the “super” superiority of the anti-Omicron immune response after 2 doses of BNT162b2 OMI compared to after 2 doses of BNT162b2 in participants ^b selected from the C4591001 study	Same as GMR estimand of G5A	Same as G5A
Exploratory		
To describe the immune response to BNT162b2 OMI or BNT162b2 given as the third and/or fourth and/or fifth dose in BNT162b2-experienced participants	For Cohort 1: at baseline, 1 month after the first study vaccination, and 1 month after the second study vaccination (Group 2 only), For Cohort 2: at baseline, 1 month and 3 months after the first study vaccination, and 1 month, 3 months, and 6 months after the last study vaccination: <ul style="list-style-type: none">• GMT at each time point• GMFRs from before the first dose of study intervention to subsequent time points• Percentages of participants with seroresponse^a at each time point	<ul style="list-style-type: none"> • SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference-strain-neutralizing titers
To describe the immune response to BNT162b2 OMI in COVID-19 vaccine-naïve participants	At baseline, 1 month and 6 months after Dose 2, and 1 month and 6 months after Dose 3: <ul style="list-style-type: none">• GMT at each time point• GMFRs from before the first dose of BNT162b2 OMI to subsequent time points• Percentages of participants with seroresponse^a at each time point	<ul style="list-style-type: none"> • SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference-strain-neutralizing titers
To describe the immune response to the reference strain and VOCs in a subset of 30 participants ^c per group		<ul style="list-style-type: none"> • SARS-CoV-2 neutralizing titers for the reference strain and VOCs
To describe the immune response to any VOCs not already specified (eg, Delta)		<ul style="list-style-type: none"> • SARS-CoV-2 neutralizing titers for any VOCs not already specified (eg, Delta)
To describe confirmed COVID-19 and severe COVID-19 cases		<ul style="list-style-type: none"> • Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases

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

- Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times \text{LLOQ}$ is considered seroresponse.
- A subset of approximately 175 participants (18 through 55 years of age) from Study C4591001 who have received 2 doses of BNT162b2 30 μg will be selected for this objective. The subset selected from Study C4591001 will include a similar percentage of participants with a positive SARS-CoV-2 infection status at baseline as Group 5 of this substudy, whenever feasible.
- This subset of participants will not contribute to the assessment of primary and secondary immunogenicity objectives.

10.10.4. Study Design

10.10.4.1. Overall Design

This is a randomized substudy composed of open-labeled and observer-blinded groups to evaluate the safety, tolerability, and immunogenicity of a 2-dose primary series of BNT162b2 OMI, and as a booster (third, fourth, or fifth) dose at investigator sites in the US and South Africa only. Participants ≥ 18 years of age to ≤ 55 years of age will be enrolled. Approximately 1420 participants will be enrolled in the study.

Participants in Cohort 1 will have completed a 2-dose primary series of BNT162b2 (30- μg doses), with their last dose 90 to 240 days prior to enrollment. Approximately 615 participants will be randomized at a ratio of 1:1:1 either to receive 1 dose (third) of BNT162b2 OMI, 2 doses (third and fourth) of BNT162b2 OMI, 4 weeks apart, or 1 dose (third) of BNT162b2. Randomization will be stratified by age (stratified as 18-30 and 31-55 years of age). Participants in Cohort 1 will remain blinded to whether they will be receiving a fourth dose through 1 month after their first dose, but the investigator and sponsor will not be blinded.

Participants in Cohort 2 will be enrolled from Study C4591001 and C4591031 Substudy A and will have completed a 2-dose primary series and received a single booster (third) dose of BNT162b2, with their last dose 90 to 180 days prior to randomization. Approximately 600 participants will be randomized at a ratio of 1:1 to receive a fourth dose of either BNT162b2 or BNT162b2 OMI at Visit 401. Participants will be offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up). Randomization will be stratified by age (stratified as 18-30 and 31-55 years of age). Cohort 2 will be observer-blinded.

In Cohort 3, 205 participants 18 through 55 years of age who are COVID-19 vaccine-naïve and have not experienced COVID-19 will be enrolled to receive 2 doses (primary series) of BNT162b2 OMI, 3 weeks apart, with a dose of BNT162b2 approximately 5 months later. If participants do not consent to receive BNT162b2 as a third dose, they will not receive a third dose. No participants should receive BNT162b2 OMI as a third dose.

A subset of 30 participants may be selected from each group to serve as a sentinel group for immunogenicity assessment. Participants in the subset will not contribute to the assessment of primary and secondary immunogenicity objectives. Immunogenicity data from these participants will be summarized separately for the exploratory objective specific for the subset. See [Section 10.10.9.5](#) for details.

Table 10 details the number of participants by cohort and group, their prior BNT162b2 experience, the vaccine that will be administered, and the number of doses administered as part of Substudy D.

Table 10. Total Number of Participants by Cohort

Cohort	Group	Prior BNT162b2 Experience	Vaccine	Number of Doses Administered as Part of Substudy D	Total Number of Participants
Cohort 1	Group 1	2 Doses	BNT162b2 OMI	1	205
	Group 2	2 Doses	BNT162b2 OMI	2	205
	Group 2b	2 Doses	BNT162b2	1	205
Cohort 2	Group 3	3 Doses	BNT162b2 OMI	1 or 2	300
	Group 4	3 Doses	BNT162b2 (and BNT162b2 OMI at Visit 404)	1 or 2	300
Cohort 3	Group 5	Naïve	BNT162b2 OMI	2	205
			BNT162b2	1	

Note: Cohorts 1 and 2 are observer-blinded. Participants in Cohort 1 will remain blinded to whether they will be receiving a fourth dose through 1 month after their first dose. Cohort 2 participants will be unblinded once they have completed Visit 404. Cohort 3 is open-labeled.

As part of protocol amendment 11, active participants in Cohort 1 and Cohort 2 at the time of this amendment will only be followed for 6 months after their last study vaccination, the protocol-specified safety reporting period. Their final visit will be V405.

10.10.4.2. Scientific Rationale for Substudy D Design

See [Section 10.10.2.1](#).

10.10.4.2.1. Diversity of Study Population

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

10.10.4.3. Justification for Dose

See [Section 4.3](#) for a justification of the BNT162b2 and BNT162b2 OMI dose used in Substudy D.

10.10.4.4. End of Study Definition

See [Section 4.4](#).

10.10.5. Study Population

Details of the master and Substudy D eligibility criteria are shown in [Section 5](#). Participants must meet all of the general inclusion and exclusion criteria as specified for the master protocol as well as Substudy D-specific inclusion and exclusion criteria.

10.10.5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants 18 to 55 years of age inclusive:

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

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in [Section 10.15](#).

4. Cohort 2: Participants who provided a serum sample at Visit 3 in Study C4591001, with Visit 3 occurring within the protocol-specified window.

Informed Consent:

5. Capable of giving personal signed informed consent as described in [Appendix 1](#), which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Other Inclusions:

6. Cohort 1: Participants who have received 2 prior doses of 30 µg BNT162b2, with the second dose being 90 to 240 days before Visit 401 (Day 1)

or

Cohort 2: Participants who have received 3 prior doses of 30 µg BNT162b2, with the third dose being 90 to 180 days before Visit 401 (Day 1).

Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

10.10.5.2. Exclusion Criteria

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

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
3. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.
4. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
5. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥ 14 days at a dose of ≥ 20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. **Cohorts 1 and 2:** prior receipt of any COVID-19 vaccine other than BNT162b2.
10. **Cohort 3 only:** prior receipt of any COVID-19 vaccine.

Other Exclusions:

11. Investigator site staff or Pfizer-BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
12. Receipt of medications intended to prevent COVID-19.
13. Participation in other studies involving study intervention within 28 days prior to study entry through and including 28 days after the last dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

10.10.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy D as detailed in [Section 5.3](#) and [Section 10.4](#).

10.10.5.4. Screen Failures

See [Section 5.4](#).

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

See [Section 5.5](#).

10.10.6. Study Intervention(s) and Concomitant Therapy

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

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg
- BNT162b2 OMI (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg

10.10.6.1. Study Intervention(s) Administered

See [Section 6.1](#) for details of BNT162b2.

Additional Intervention Name	BNT162b2 OMICRON (B.1.1.529) (BNT162 RNA-LNP vaccine utilizing modRNA)
Type	Vaccine
Dose Formulation	modRNA
Unit Dose Strength(s)	250 µg/0.5 mL
Dosage Level(s)	30 µg
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement.

10.10.6.1.1. Administration

For Cohorts 1 and 2, participants will receive 1 dose of study intervention as allocated by the IRT at Visit 401 (third or fourth dose) in accordance with the substudy's SoA ([Section 10.10.1.3](#)). Group 2 participants will receive a second dose of BNT162b2 OMI at Visit 402. Group 3 and Group 4 participants may receive a dose of BNT162b2 OMI at Visit 404.

For Cohort 3, COVID-19 vaccine-naïve participants will receive 1 dose of BNT162b2 OMI at Visit 501 and Visit 502, and 1 dose of BNT162b2 at Visit 506. Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

10.10.6.1.2. Preparation and Dispensing

Study intervention will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way as to ensure that the participants in Cohorts 1 and 2 remain blinded. Cohort 3 is open-labeled.

10.10.6.2. Measures to Minimize Bias: Randomization and Blinding

10.10.6.2.1. Blinding of Site Personnel

In Cohort 1 (Groups 1 and 2b) and Cohort 2, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The group of participants who will be enrolled to receive a third and fourth dose of BNT162b2 OMI (Group 2 of Cohort 1) will remain blinded to whether they will be receiving a fourth dose, through 1 month after their first dose of BNT162b2 OMI, but the investigator and sponsor will not be blinded.

Participants in Cohort 2 will be unblinded to confirm the vaccine received once they have completed Visit 404 (3 months after Substudy D Vaccination 1).

10.10.6.2.2. Blinding of the Sponsor

The majority of sponsor/Pfizer staff will be blinded to study intervention allocation for Cohort 1 (Groups 1 and 2b) and Cohort 2. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor/Pfizer staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.
- An unblinded team supporting interactions with, and analyses for, the DMC (see [Section 10.9.9.4.2](#)). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.
- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of

statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.

Participants in Cohort 1 (Groups 1 and 2b) may be unblinded to confirm the vaccine received once they have completed Visit 404 (3 months after Substudy D Vaccination 1). Cohort 2 participants will be unblinded once they have completed Visit 404. Since these are the only participants still blinded at this time, the study team will also become unblinded to all participants' original study intervention allocation at this time.

10.10.6.2.3. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

10.10.6.3. Study Intervention Compliance

See [Section 6.4](#).

10.10.6.4. Dose Modification

See [Section 6.5](#).

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

See [Section 6.6](#).

10.10.6.6. Treatment of Overdose

See [Section 6.7](#).

10.10.6.7. Concomitant Therapy

See [Section 6.8](#).

10.10.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See [Section 7](#).

10.10.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 250 mL for those participants who receive 1 dose and 350 mL for those who receive 2 doses. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of up to approximately 735 mL for those participants who receive 1 dose and 785 mL for those who receive 2 doses.

For those participants enrolled in Cohort 3, COVID-19 vaccine-naïve participants who will receive 2 doses of BNT162b2 OMI followed by 1 dose of BNT162b2, the total blood sampling volume for individual participants is up to approximately 350 mL. Those participants in the cohort who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of up to approximately 1195 mL.

For all participants, other 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 60 consecutive days.

10.10.8.1. Surveillance for COVID-19

If, at any time, a participant develops acute respiratory illness (see [Section 10.7.8.5.5.1](#)), for the purposes of the study he or she will be considered to potentially have COVID-19 illness. 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 collection of a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA-approved under EUA and Pfizer-validated), 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 10.7.8.5.5.1](#)) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

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

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

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.
- Confirmed severe COVID-19 (FDA definition⁴⁵): confirmed COVID-19 and presence of at least 1 of the following:
 - Clinical signs at rest indicative of severe systemic illness (RR \geq 30 breaths per minute, HR \geq 125 beats per minute, SpO₂ \leq 93% on room air at sea level, or PaO₂/FiO₂ $<$ 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 definition⁴⁶): 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.

10.10.8.2. Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the [SoA](#). The test to be performed will be the SARS-CoV-2 neutralizing assay (reference strain and Omicron strain). Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory.

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each group for evaluation of boostability and protection against Omicron and the reference strain (both BNT162b2-experienced and BNT162b2-naïve) at select sites for isolation of PBMCs. These samples will be used to describe B-cell and T-cell responses to Omicron and the reference strain. A blood sample of ~5 mL for HLA typing will also be obtained.

10.10.8.3. Safety Assessments

See [Section 8.2](#).

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

See [Section 8.3](#).

10.10.8.5. Specified Genetics

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

See [Appendix 16](#) for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

10.10.8.6. Substudy D Procedures

10.10.8.6.1. Administration of Additional Dose(s) of BNT162b2 or BNT162b2 OMI (Cohort 1)

10.10.8.6.1.1. Visit 401 – Substudy D Vaccination (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).

As Cohort 1 is observer-blinded, the blinded and unblinded roles should still be maintained to ensure the integrity of the blind:

- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and fever (COVID-19 surveillance) and provide instructions on their use.
- Explain the e-diary technologies available for this study (see [Section 8.2.4](#)), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
- Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.
- Provide instructions on COVID-19 illness e-diary completion and ask the participant 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 10.10.8.6.4](#) for further details. Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - 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 to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.10.8.6.7](#)).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the reactogenicity e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.10.8.6.1.2. Visit 402 – 1-Month Follow-Up Visit (After Substudy D Vaccination 1) (28 to 35 Days After Visit 401)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity testing.

- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

Only if the participant is to receive a second dose of BNT162b2 OMI (Substudy D Vaccination 2):

- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Measure the participant's body temperature.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

Note: a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. Please see [Section 7.1](#).

- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of BNT162b2 OMI into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant has a self-swab kit.
- Remind the participant of the e-diary technologies available for this study (see [Section 10.10.8.6.5](#)). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed 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).

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see [Section 10.10.8.6.8](#)):
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - 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 to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- 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.

10.10.8.6.1.3. Visit 403 – 1-Month Follow-Up Visit (After Substudy D Vaccination 2) (28 to 35 Days After Visit 402): Only for Those Participants Who Receive Substudy D Vaccination 2

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 5.3](#).

- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.1.4. Visit 404 – 3-Month Follow-Up Visit (85 to 95 Days After Visit 401, or 85 to 95 Days After Visit 402 for Those Participants Who Receive Substudy D Vaccination 2)

- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Participants in Cohort 1 (Groups 1 and 2b) may be unblinded to confirm the vaccine received once they have completed Visit 404 (3 months after Substudy D Vaccination 1). Since these are the only participants still blinded at this time, the study team will also become unblinded to all participants' original study intervention allocation at this time.

10.10.8.6.1.5. Visit 405 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 401, or 175 to 189 Days After Visit 402 for Those Participants Who Receive Substudy D Vaccination 2)

For participants who have already completed V405 at the time of protocol amendment 11, they will be informed by the investigator site staff of study completion and that no further visits are required.

- Record AEs as described in [Section 8.3](#)
- Collect a blood sample for immunogenicity testing.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant 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.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.10.8.6.2. Administration of Additional Dose(s) of BNT162b2 or BNT162b2 OMI (Cohort 2)

Participants who do not provide consent to receive a dose of BNT162b2 OMI at Visit 404 will remain on the single-dose visit schedule.

10.10.8.6.2.1. Visit 401 – Substudy D Vaccination (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).

- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).

As Cohort 2 is observer-blinded, the blinded and unblinded roles should still be maintained to ensure the integrity of the blind:

- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and fever (COVID-19 surveillance) and provide instructions on their use.
- Explain the e-diary technologies available for this study (see [Section 8.2.4](#)), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
- Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.
- Provide instructions on COVID-19 illness e-diary completion and ask the participant 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 10.10.8.6.4](#) for further details. Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - 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 to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.10.8.6.7](#)).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the reactogenicity e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.10.8.6.2.2. Visit 402 – 1-Month Follow-Up Visit (After Substudy D Vaccination 1) (28 to 35 Days After Visit 401)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).

- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.2.3. Visit 404 – 3-Month Follow-Up Visit (85 to 95 Days After Visit 401, or 85 to 123 Days After Visit 401 for Those Participants Who Consent to Receive Substudy D Vaccination 2)

NOTE: Participants in Cohort 2 will be unblinded to confirm the vaccine received once they have **COMPLETED** Visit 404 (3 months after Substudy D Vaccination 1). Since these will be the only participants still blinded at this time, the study team will also become unblinded to all participants' original study intervention allocation at this time.

- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- 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 respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

Only if the participant consents to receive a dose of BNT162b2 OMI (Substudy D Vaccination 2):

NOTE: Voluntary, written, study-specific informed consent will be obtained from the participant before the participant receives a dose of BNT162b2 OMI at Visit 404. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before the participant receives a dose of BNT162b2 OMI.

NOTE: Participants who do not provide consent to receive a dose of BNT162b2 OMI at Visit 404 will remain on the single-dose visit schedule.

- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Measure the participant's body temperature.

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

Note: a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. Please see [Section 7.1](#).

- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of BNT162b2 OMI into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant has a self-swab kit.
- Remind the participant of the e-diary technologies available for this study (see [Section 10.10.8.6.5](#)). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed 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).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see [Section 10.10.8.6.8](#)):
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - 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 to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- 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.
- Participants in Cohort 2 will be unblinded to confirm the vaccine received once they have completed Visit 404 (3 months after Substudy D Vaccination 1). Since these are the only participants still blinded at this time, the study team will also become unblinded to all participants' original study intervention allocation at this time.

10.10.8.6.2.4. Visit 404a – 7-Day Follow-Up Visit (After Substudy D Vaccination 2) (5 to 9 Days After Visit 404): Only for Those Participants Who Receive Substudy D Vaccination 2

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.10.8.6.7](#)).

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.2.5. Visit 404b – 1-Month Follow-Up Visit (After Substudy D Vaccination 2) (28 to 35 Days After Visit 404): Only for Those Participants Who Receive Substudy D Vaccination 2

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.

- 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.

10.10.8.6.2.6. Visit 404c – 3-Month Follow-Up Visit (After Substudy D Vaccination 2) (85 to 95 Days After Visit 404): Only for Those Participants Who Receive Substudy D Vaccination 2

- Record AEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- 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 respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.2.7. Visit 405 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 401, or 175 to 189 Days After Visit 404 for Those Participants Who Receive Substudy D Vaccination 2)

For participants who have already completed V405 at the time of protocol amendment 11, they will be informed by the investigator site staff of study completion and that no further visits are required.

- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity testing.

- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant 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.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.10.8.6.3. Administration of BNT162b2 OMI to COVID-19 Vaccine–Naïve Participants (Cohort 3)

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new group of participants will be enrolled who are COVID-19 vaccine-naïve and have not experienced COVID-19. They will receive 2 doses (primary series) of BNT162b2 OMI, separated by 21 days, with a third dose approximately 5 months later.

10.10.8.6.3.1. Visit 501 – Vaccination 1 (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.

- Site staff member(s) will dispense/administer 1 dose of BNT162b2 OMI into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual 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.
- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and fever (COVID-19 surveillance) and provide instructions on their use.
- Explain the e-diary technologies available for this study (see [Section 10.10.8.6.5](#)), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
- Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.
- Provide instructions on COVID-19 illness e-diary completion and ask the participant 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 10.10.8.6.4](#) for further details. Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - 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 to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.10.8.6.7](#)).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and 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.

10.10.8.6.3.2. Visit 502 – Vaccination 2 (19 to 23 Days After Visit 501)

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.

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see [Section 10.10.5](#)).

Note: a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. Please see [Section 7.1](#).

- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 10.10.5.5](#).
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 OMI into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual 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.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if 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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - 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 to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.10.8.6.7](#)).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and 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.

10.10.8.6.3.3. Visit 503 – 1-Week Follow-Up Visit (After Vaccination 2) (6 to 8 Days After Visit 502): Only for Those Participants Who Are Part of the Group for Description of Cell-Mediated Immune Response

- Record AEs as described in [Section 8.3](#)
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity testing.
- Collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.10.8.6.7](#)).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.

- 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.

10.10.8.6.3.4. Visit 504 – 1-Month Follow-Up Visit (After Vaccination 2) (28 to 35 Days After Visit 502)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.3.5. Visit 505 – 3-Month Follow-Up Visit (After Vaccination 2) (85 to 95 Days After Visit 502)

- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#)
- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.10.8.6.3.6. Visit 506 – 6-Month Follow-Up Visit (After Vaccination 2) (150 to 199 Days After Visit 502) and Administration of Vaccination 3

- Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.

- Discuss contraceptive use as described in [Section 5.3](#).
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Measure the participant's body temperature.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

Note: a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. Please see [Section 7.1](#).

- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process. Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Remind the participant of the e-diary technologies available for this study (see [Section 10.10.8.6.5](#)). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination, and, if utilized, the COVID-19 illness e-diary (to be completed 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).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see [Section 10.8.8.3.7](#)):
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).

- 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 to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.10.8.6.3.7. Visit 507 – 1-Month Follow-Up Visit (After Vaccination 3) (28 to 35 Days After Visit 506)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.10.8.6.4.1](#).
- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

10.10.8.6.3.8. Visit 508 – 6-Month Follow-Up Visit (After Vaccination 3) (175 to 189 Days After Visit 506)

- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant 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.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.10.8.6.4. COVID-19 Surveillance (All Substudy D Participants)

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

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;

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

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs.

Participants may utilize a COVID-19 illness e-diary through an application (see [Section 10.10.8.6.5](#)) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

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

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant 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:

- Record AEs, as appropriate as described in [Section 8.3](#). Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if the visit is conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship 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 \geq 30 breaths per minute, HR \geq 125 beats per minute, SpO₂ \leq 93% on room air at sea level, or PaO₂/FiO₂ <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 C-reactive protein
 - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
 - Number and type of any healthcare contact; duration of hospitalization and ICU stay
 - Death
- Complete the source documents.
 - The investigator or an authorized designee completes the CRFs.

10.10.8.6.5. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant 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 and the study site staff will be established. The participant 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:

- Contact with the investigator, including the ability of the participant to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- If a participant is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

10.10.8.6.6. SARS-CoV-2 NAAT Results

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

- Visits 401, 402 (for Group 2 participants who receive a second dose of BNT162b2 OMI only), 404 (for Group 3 and Group 4 participants who receive a dose of BNT162b2 OMI at Visit 404 only), 501, 502, and 506: To determine whether a participant will be included in immunogenicity analyses of those with no serological or virological evidence (up to 1 month after receipt of the third, fourth, or fifth dose to BNT162b2-experienced participants, or as a 2-dose series to COVID-19 vaccine-naïve participants) of past SARS-CoV-2 infection.
- 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 Visit 401 and Visit 501 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

10.10.8.6.7. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably 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.

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

If a Grade 3 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever ([Section 8.2.4.4](#)) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever ([Section 8.2.4.4](#)) 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 recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

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

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

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

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in [Section 8.2.4.2](#).
- Assess systemic events (if present) in accordance with the grades provided in [Section 8.2.4.3](#).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

10.10.9. Statistical Considerations for Substudy D

See [Section 9](#) for master protocol statistical considerations and substudy specifics below.

10.10.9.1. Statistical Hypotheses

10.10.9.1.1. Estimands

The estimands corresponding to the primary and secondary objectives are described in the table in [Section 10.10.3](#).

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

10.10.9.1.2. Statistical Hypotheses

The primary immunogenicity objectives for Cohort 2 and Cohort 3 are to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response induced by BNT162b2 OMI relative to the anti-Omicron immune response elicited by BNT162b2. Each primary objective for Cohort 2 and Cohort 3 will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

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

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

- $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after BNT162b2 OMI;
- $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after BNT162b2.

- The second null hypothesis (H_0) is

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

where -5% is the noninferiority margin for seroresponse and

- p_1 is the percentage of participants with seroresponse to the Omicron strain at 1 month after BNT162b2 OMI;
- p_2 is the percentage of participants with seroresponse to the Omicron strain at 1 month after BNT162b2.

Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times \text{LLOQ}$ is considered seroresponse.

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

The secondary objectives of “super” superiority will be evaluated using a 1.5-fold margin for GMR. “Super” superiority for GMR will be established if the lower limit of the 2-sided 95% CI for the GMR is greater than 1.5.

10.10.9.1.3. Multiplicity Adjustment

The immunogenicity objectives for BNT162b2-experienced participants who completed a 2-dose primary series of BNT162b2 prior to enrollment in this study (Cohort 1), BNT162b2-experienced participants who completed a 2-dose primary series and a booster dose of BNT162b2 prior to enrollment in this study (Cohort 2), and COVID-19 vaccine-naïve participants (Cohort 3) will be evaluated independently. The 3 cohorts (2-dose BNT162b2-experienced, 3-dose BNT162b2-experienced, and COVID-19 vaccine-naïve individuals) are different populations with different objectives. The 3 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied to the immunogenicity assessments of the 3 populations.

No multiplicity adjustment is needed for Cohort 1 as there is no statistical hypothesis in Cohort 1.

For each population in Cohort 2 and Cohort 3, the objectives will be evaluated in sequential order as listed below using a 1-sided alpha of 0.025:

Cohort 2 (Groups 3 and 4): G3vG4A ® G3vG4B

Cohort 3 (Group 5): G5A ® G5B

For objectives involving 2 hypotheses, hypotheses based on GMR and seroresponse rate difference will be assessed sequentially in the order as stated. Both hypotheses within the objective must be established before assessing the next objective in the sequence. Therefore, the overall type I error is fully controlled for each of these 2 populations.

10.10.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention(s) to which they are randomized or assigned, have a 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 randomized/assigned participants who receive at least 1 dose of the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive at least 1 dose of the study intervention.

10.10.9.3. Statistical Analyses

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

10.10.9.3.1. General Considerations

Refer to [Section 9.3.1](#) for general considerations of statistical analyses.

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

Endpoint	Statistical Analysis Methods
Safety	<ul style="list-style-type: none"> Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each study vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after the last study vaccination will be provided for each vaccine group.
Immunogenicity	<p>For each primary immunogenicity estimand described in Section 10.10.3</p> <ul style="list-style-type: none"> GMRs and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.2.3. The percentages of participants with seroresponse for each group will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method (see Section 9.3.1.1). For Cohort 1, only participants with evidence of past SARS-CoV-2 infection will be included in the analysis. For Cohort 2, only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention) of past SARS-CoV-2 infection will be included in the analysis. For Cohort 2 and Cohort 3, superiority based on GMR will be established if the lower bound of the 2-sided 95% CI for the GMR is >1; noninferiority based on seroresponse rate difference will be established if the lower bound of the 2-sided 95% CI for the difference in percentage is greater than -5%.

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

Endpoint	Statistical Analysis Methods
Immunogenicity	<p>For each secondary immunogenicity estimand described in Section 10.10.3</p> <ul style="list-style-type: none"> • GMR and the associated 2-sided 95% CIs, the percentages of participants with seroresponse, and the difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using same method as for the primary immunogenicity objectives. • “Super” superiority will be evaluated using criteria described in Section 10.10.9.1.2 and Section 10.10.9.1.3.

10.10.9.3.4. Exploratory Endpoint(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	<p>GMTs and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers</p> <p>Percentages of participants with seroresponse to Omicron or the reference strain</p> <p>Cohort 1: At baseline, 1 month after the first study vaccination, and 1 month after the second study vaccination (Group 2 only),</p> <p>Cohort 2: At baseline, 1 month and 3 months after the first study vaccination, and 1 month, 3 months, and 6 months after the last study vaccination,</p> <p>Cohort 3: At baseline, 1 month and 6 months after Dose 2, and 1 month and 6 months after Dose 3,</p> <ul style="list-style-type: none"> • GMTs at each of the above time points and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers from baseline (before the first study vaccination received in this study) to each of the above postvaccination time points, along with the associated 2-sided 95% CIs, will be provided for each vaccine group using the statistical method described in Section 9.3.1.2.1 and Section 9.3.1.2.2. • The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group.

Endpoint	Statistical Analysis Methods
	<p>GMTs and GMFRs of SARS-CoV-2 reference strain and VOCs for the subset of 30 participants per group</p> <p>Percentages of participants with seroresponse to reference strain and VOCs for the subset of 30 participants per group</p> <ul style="list-style-type: none"> GMTs, GMFRs, and percentages of participants with seroresponse for the subset of 30 participants per group, along with the associated 95% CIs, will be calculated using same method as described above. <p>GMTs for any VOCs not already specified, after any dose of BNT162b2 OMI or BNT162b2</p> <ul style="list-style-type: none"> GMTs of VOC-neutralizing titers, along with the associated 2-sided 95% CIs, will be provided at specific time points for each group. GMFRs and GMRs of VOC-neutralizing titers to reference-strain-neutralizing titers may also be calculated along with the associated 2-sided 95% CIs.
COVID-19 cases	Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized.
Cell-mediated immune response	The cell-mediated immune response and additional humoral immune response parameters to the reference strain and Omicron will be summarized at each time point for the subset of participants with PBMC samples collected in each group.

10.10.9.4. Interim Analyses

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

10.10.9.4.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Safety data through 1 month after the first study vaccination received in this study for Groups 1, 2b, 3, and 4 or through 1 month after the second study vaccination received in this study for Groups 2 and 5.
- Immunogenicity data for the subset of 30 participants per group.

- Immunogenicity data through 1 month after the first study vaccination (for Groups 1, 2b, 3, and 4) or 1 month after the second study vaccination (for Groups 2 and 5) received in this study for participants enrolled in this study and through 1 month after Dose 2 for the comparator group from the C4591001 study.
- Complete safety and immunogenicity analysis approximately 6 months after the last study vaccination for each group.

Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses conducted while the study is ongoing will be performed by an unblinded team.

10.10.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail. The DMC will be responsible for ongoing monitoring of the safety data throughout the study according to the charter.

The recommendations made by the DMC will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, investigators as appropriate.

10.10.9.5. Sample Size Determination

The sample size for Groups 3 and 4 is based on consideration of an acceptable safety database. A subset of 30 participants from each group may be selected as a sentinel group for separate assessment of immune response defined in an exploratory objective. The subset may be the first 30 participants selected for operational expedience or a random sample selection depending on the enrollment status. A random sample of approximately 100 participants with evidence of past SARS-CoV-2 infection from each of Groups 1, 2, and 2b selected from the remaining approximately 175 participants will be used for evaluation of the primary immunogenicity objectives in each group for Cohort 1. A random sample of 175 participants from each of Groups 3 and 4 selected from the remaining approximately 270 participants, and the remaining approximately 175 participants in Group 5, will be used for evaluation of the primary and secondary immunogenicity objectives in each group for Cohort 2 and Cohort 3. The same number of participants for Group 5 will be selected from the C4591001 study as a control group for the immunogenicity evaluation.

Assuming a 35% nonevaluable and prior SARS-CoV-2 infection rate, approximately 114 evaluable participants in each group will contribute to the immunogenicity evaluation. The superiority and noninferiority evaluation based on GMR and seroresponse rate difference will each be performed at 1-sided alpha level of 0.025 as described in [Section 10.10.9.1.3](#).

Superiority Immunogenicity Objectives

For comparisons based on GMR, common assay standard deviations at 1 month after the third or fourth dose or 1 month after Dose 2 in log scale is assumed to be 0.93 based on data observed in the C4591001 study. If the true GMR of Omicron-neutralizing titer after BNT162b2 OMI to after BNT162b2 is 1.5, 114 evaluable participants per group will provide 90.6% power to declare superiority. If the true GMR is 2.5, the study will have 98.5% power to declare “super” superiority using a 1.5-fold margin.

For comparisons based on seroresponse rate difference, if the seroresponse rate is 80% in the BNT162b2 OMI group and 60% in the BNT162b2 group, the study has 98.6% power to demonstrate noninferiority using a 5% margin.

For safety outcomes, Table 11 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 1%, with 300 participants in a vaccine group, there is 95% probability of observing at least 1 AE.

Table 11. Probability of Observing at 1 Least AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=30	N=205	N=300	N=915	N=1420
0.01%	0.003	0.02	0.03	0.09	0.13
0.02%	0.006	0.04	0.06	0.17	0.25
0.05%	0.01	0.10	0.14	0.37	0.51
0.10%	0.03	0.19	0.26	0.60	0.76
0.20%	0.06	0.34	0.45	0.84	0.94
0.50%	0.14	0.64	0.78	0.99	>0.99
1.00%	0.26	0.87	0.95	>0.99	>0.99
2.00%	0.45	0.98	>0.99	>0.99	>0.99
5.00%	0.79	>0.99	>0.99	>0.99	>0.99
10.0%	0.96	>0.99	>0.99	>0.99	>0.99

10.11. Appendix 11: Substudy E

10.11.1. Substudy Summary

10.11.1.1. Substudy Synopsis

See [Section 1.1](#) for a synopsis of Substudy E.

10.11.1.2. Schema

Visit Number	Screening	601	601A	602	603	604	605
Visit Description	Screening ^a	4 th Dose of BNT162b2, BNT162b2 OMI, or Combination BNT162b2 and BNT162b2 OMI	3 Days After 4 th Vaccination ^a	7 Days After 4 th Vaccination	1 Month After 4 th Vaccination	3 Months After 4 th Vaccination	6 Months After 4 th Vaccination
	ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9		ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9				
Participants having received 3 prior doses of 30 µg BNT162b2 5-12 months prior to randomization		30-µg OR 60-µg dose					
Blood draw for immunogenicity assessment/PBMC isolation ^b		50 mL/120 mL		50 mL/120 mL	50 mL/120 mL	50 mL/120 mL	50 mL/120 mL
Blood draw for troponin levels	10 mL		10 mL				

- a. Only for sentinel-cohort participants 18 to 55 years of age (Groups 7 to 9).
b. Additional 120 mL for PBMC isolation (and 5 mL for HLA typing at Visit 601) is for select expanded-enrollment participants (~30 per group for Groups 1 to 6, and ~90 across all groups for Groups 7 to 9) at select sites only. Sentinel-cohort participants will not have samples collected for PBMC isolation/HLA typing. See [Section 10.11.8.2](#).

10.11.1.3. Schedule of Activities for Substudy E

Visit Number	Screening	601	601A	602	603	604	605	Unplanned
Visit Description	Screening ^a	Vaccination	3-Day Follow-Up Visit After Vaccination ^a	1-Week Follow-Up Visit After Vaccination	1-Month Follow-Up Visit After Vaccination	3-Month Follow-Up Visit After Vaccination	6-Month Follow-Up Visit After Vaccination	Potential COVID-19 Illness Visit ^b
Visit Window (Days)	0 to 14 Days Before Visit 601	Day 1 ^c	2 to 4 Days After Visit 601	6 to 8 Days After Visit 601	28 to 35 Days After Visit 601	85 to 95 Days After Visit 601	175 to 189 Days After Visit 601	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9		ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9					
Obtain informed consent	X	X ^d						
Obtain the participant's prior study and participant number (if applicable)	X	X ^d						
Assign participant number	X	X ^d						
Obtain demography and medical history data	X	X ^d						
Perform clinical assessment ^c	X	X						
Measure height and weight	X	X						
Measure temperature (body)		X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X	X	X			
Collect nonstudy vaccine information	X	X	X	X	X	X	X	
Collect prohibited medication use			X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X ^d			X	X	X	
Confirm eligibility	X	X						
Review temporary delay criteria		X						

Visit Number	Screening	601	601A	602	603	604	605	Unplanned
Visit Description	Screening ^a	Vaccination	3-Day Follow-Up Visit After Vaccination ^a	1-Week Follow-Up Visit After Vaccination	1-Month Follow-Up Visit After Vaccination	3-Month Follow-Up Visit After Vaccination	6-Month Follow-Up Visit After Vaccination	Potential COVID-19 Illness Visit ^b
Visit Window (Days)	0 to 14 Days Before Visit 601	Day 1 ^c	2 to 4 Days After Visit 601	6 to 8 Days After Visit 601	28 to 35 Days After Visit 601	85 to 95 Days After Visit 601	175 to 189 Days After Visit 601	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9		ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9					
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation ^f		~120 mL		~120 mL	~120 mL	~120 mL	~120 mL	
Collect blood sample for HLA typing ^f		~5 mL						
Collect a blood sample for troponin testing	10 mL		10 mL					
Obtain nasal (midturbinate) swab		X						X
Obtain the participant's vaccine vial allocation using the IRT system		X						
Administer study intervention		X						
Assess acute reactions for at least 30 minutes after study intervention administration		X						
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X						
Provide/ensure the participant has a thermometer and measuring device		X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		X→	X→	X→				

Visit Number	Screening	601	601A	602	603	604	605	Unplanned
Visit Description	Screening ^a	Vaccination	3-Day Follow-Up Visit After Vaccination ^a	1-Week Follow-Up Visit After Vaccination	1-Month Follow-Up Visit After Vaccination	3-Month Follow-Up Visit After Vaccination	6-Month Follow-Up Visit After Vaccination	Potential COVID-19 Illness Visit ^b
Visit Window (Days)	0 to 14 Days Before Visit 601	Day 1 ^c	2 to 4 Days After Visit 601	6 to 8 Days After Visit 601	28 to 35 Days After Visit 601	85 to 95 Days After Visit 601	175 to 189 Days After Visit 601	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9		ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates			X	X	X			
Collect AEs and SAEs as appropriate	X	X	X	X	X ^g	X ^g	X ^g	X
Collect e-diary or assist the participant to delete application							X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X

Visit Number	Screening	601	601A	602	603	604	605	Unplanned
Visit Description	Screening ^a	Vaccination	3-Day Follow-Up Visit After Vaccination ^a	1-Week Follow-Up Visit After Vaccination	1-Month Follow-Up Visit After Vaccination	3-Month Follow-Up Visit After Vaccination	6-Month Follow-Up Visit After Vaccination	Potential COVID-19 Illness Visit ^b
Visit Window (Days)	0 to 14 Days Before Visit 601	Day 1 ^c	2 to 4 Days After Visit 601	6 to 8 Days After Visit 601	28 to 35 Days After Visit 601	85 to 95 Days After Visit 601	175 to 189 Days After Visit 601	Optimally Within 3 Days After Potential COVID-19 Illness Onset
	ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9		ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9					
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs		X		X	X	X		

Abbreviations: HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell.

- Only for sentinel-cohort participants 18 to 55 years of age in Groups 7 to 9. The Screening Visit can occur over more than 1 day.
- The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
- The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
- These Visit 601 procedures are not required for the Group 7, 8, and 9 sentinel-cohort participants, as they will be completed at the screening visit.
- Including, if indicated, a physical examination.
- Additional 120 mL for PBMC isolation (and 5 mL for HLA typing at Visit 601) is for select expanded-enrollment participants (~30 per group for Groups 1 to 6, and ~90 across all groups for Groups 7 to 9) at select sites only. Sentinel-cohort participants will not have samples collected for PBMC isolation/HLA typing. See [Section 10.11.8.2](#).
- Any AEs occurring up to 48 hours after the blood draw must be recorded (see [Section 8.3.1](#)).

10.11.2. Introduction

10.11.2.1. Study Rationale

The SARS-CoV-2 variant B.1.1.529, also known as Omicron, is currently the dominant variant in many countries and within the US is responsible for 98.3% of sequenced COVID-19 cases as of 08 January 2022.²⁵ Current data note that the vaccine effectiveness against hospitalization is 88% (78%-93%) for Omicron after 3 doses of vaccine.²⁶ However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant. The addition of a higher dose booster may improve protection, particularly in older individuals, with increased longevity of an immune response, provided it has a tolerable safety profile.²⁷ Therefore, Substudy E has been designed to evaluate high-dose BNT162b2 OMI (60 µg), high-dose BNT162b2 (60 µg), and a high-dose combination of BNT162b2 OMI and BNT162b2 (30 µg of each), compared to BNT162b2 OMI 30 µg, BNT162b2 30 µg, and a combination of BNT162b2 OMI and BNT162b2 (15 µg of each), given as a fourth dose.

See [Section 2.2](#) for the study background.

10.11.2.2. Benefit/Risk Assessment

A tolerability profile of a 60-µg dose of BNT162b2 has yet to be established. However, BNT162b1 (a candidate RNA-LNP vaccine tested in clinical trial C4591001 utilizing a nucleoside-modified messenger RNA similar to BNT162b2 but instead of encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein, BNT162b1 encodes the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain) was studied in adults 18 to 55 years of age at dose levels of 50 µg, 60 µg, and 100 µg. In one study, 60 participants were vaccinated with BNT162b1. Twelve participants for each of the dose level groups (1 µg, 10 µg, 30 µg, 50 µg, and 60 µg) were to receive the first dose on Day 1 and a second dose on Day 22. Due to the tolerability observed in participants after 2 doses of 50 µg and after reviewing the totality of the data available, including the local and systemic reactogenicity data (such as the increasing number of severe [Grade 3] systemic reactions reported with ascending dose), a second dose of 60 µg was not administered.^{37,47} Another study investigated BNT162b1 at 10 µg, 30 µg, and 100 µg. Participants in this study were not administered the second dose of 100 µg because of the increased reactogenicity profile seen after a single dose at 100 µg and in participants who received 2 doses of 30 µg.³⁸ In light of better tolerability of BNT162b2 (compared to BNT162b1), and better tolerability in older adults (compared to younger adults), the potential benefit of a 60-µg dose of BNT162b2 is likely to outweigh the risk.

10.11.2.2.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy E may be:

- Receipt of a fourth dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic, particularly against new variant-associated infection and disease.

- Contributing to research to help others in a time of global pandemic.

10.11.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety		
<ul style="list-style-type: none"> • To describe the safety and tolerability profile of BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants >55 years of age 	<p>In participants receiving at least 1 dose of study intervention, the percentage of participants reporting:</p> <ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • To describe the safety and tolerability profile of BNT162b2 OMI 60 µg and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants 18-55 years of age 	<p>In participants receiving at least 1 dose of study intervention, the percentage of participants reporting:</p> <ul style="list-style-type: none"> • 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 • Percentage of participants with elevated troponin I levels before and 3 days after study vaccination (sentinel cohort only) 	<ul style="list-style-type: none"> • 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 • Troponin I level (sentinel cohort only)
Primary Immunogenicity		
<p>G3vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age</p>	<p>In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection:</p> <ul style="list-style-type: none"> • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse^a to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI 30 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants 	<ul style="list-style-type: none"> • SARS-CoV-2 Omicron-neutralizing titers

Objectives	Estimands	Endpoints
G4vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	<p>In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection:</p> <ul style="list-style-type: none"> GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants The difference in percentages of participants with seroresponse^a to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI 60 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants 	<ul style="list-style-type: none"> SARS-CoV-2 Omicron-neutralizing titers
G5vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	<p>In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection:</p> <ul style="list-style-type: none"> GMR of the Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants The difference in percentages of participants with seroresponse^a to the Omicron strain at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants 	<ul style="list-style-type: none"> SARS-CoV-2 Omicron-neutralizing titers
G6vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	<p>In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection:</p> <ul style="list-style-type: none"> GMR of the Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants The difference in percentages of participants with seroresponse^a to the Omicron strain at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants 	<ul style="list-style-type: none"> SARS-CoV-2 Omicron-neutralizing titers

Objectives	Estimands	Endpoints
Secondary Immunogenicity		
G5vG1B: To demonstrate the noninferiority of anti-reference-strain immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: <ul style="list-style-type: none"> GMR of the reference-strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants 	<ul style="list-style-type: none"> SARS-CoV-2 reference-strain–neutralizing titers
G6vG1B: To demonstrate the noninferiority of anti-reference strain immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: <ul style="list-style-type: none"> GMR of the reference-strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants 	<ul style="list-style-type: none"> SARS-CoV-2 reference-strain–neutralizing titers
To demonstrate the “super” superiority of anti-Omicron immune responses after 1 dose of BNT162b2 OMI at 30 µg (G3vG1B), BNT162b2 OMI at 60 µg (G4vG1B), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (G5vG1C), or bivalent BNT162b2 and BNT162b2 OMI at 60 µg (G6vG1C) compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	Same as GMR estimand of G3vG1A, G4vG1A, G5vG1A, G6vG1A	<ul style="list-style-type: none"> SARS-CoV-2 Omicron-neutralizing titers
• Exploratory		
To describe the immune response to BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose in BNT162b2-experienced participants >55 years of age	<ul style="list-style-type: none"> GMT at each time point GMFRs from before the study vaccination to subsequent time points Percentages of participants with seroresponse^a at each time point 	<ul style="list-style-type: none"> SARS-CoV-2 Omicron-neutralizing titers SARS-CoV-2 reference-strain–neutralizing titers
To describe the immune response to bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg), BNT162b2 OMI 60 µg, and BNT162b2 30 µg ^b given as a fourth dose in BNT162b2-experienced participants 18 to 55 years of age	<ul style="list-style-type: none"> GMT at each time point GMFRs from before the study vaccination to subsequent time points Percentages of participants with seroresponse^a at each time point 	<ul style="list-style-type: none"> SARS-CoV-2 Omicron-neutralizing titers SARS-CoV-2 reference-strain–neutralizing titers

Objectives	Estimands	Endpoints
To describe the immune response to the reference strain and VOCs for participants ^c in sentinel cohorts of each age group		<ul style="list-style-type: none"> SARS-CoV-2 neutralizing titers for the reference strain and VOCs
To describe the immune response to any VOCs not already specified in each age group		<ul style="list-style-type: none"> SARS-CoV-2 neutralizing titers for any VOCs not already specified
To describe confirmed COVID-19 and severe COVID-19 cases in each age group		<ul style="list-style-type: none"> Confirmed COVID-19 cases Confirmed severe COVID-19 cases Strain sequencing of COVID-19 cases
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and Omicron in a subset of participants with PBMC samples collected in each group for each age group		

- Seroresponse is defined as achieving ≥ 4 -fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times$ LLOQ is considered seroresponse.
- A subset of the youngest 150 participants from the >55 -year-old group in Substudy E who have received bivalent BNT162b2 30 μg as a fourth dose will be selected for this objective.
- This subset of participants will not contribute to the assessment of primary immunogenicity objectives.

10.11.4. Study Design

10.11.4.1. Overall Design

This is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 μg), high-dose BNT162b2 OMI (60 μg), and a high-dose combination of BNT162b2 and BNT162b2 OMI at 60 μg (30 μg each), given as a single dose. Approximately 1920 participants >55 years of age and 990 participants 18 to 55 years of age who have received 3 prior doses of BNT162b2 (30- μg doses), with the most recent dose being 5 to 12 months (150 to 360 days) prior to randomization, will be enrolled at investigator sites in the US only. Participants >55 years of age will be randomized at a ratio of 1:1:1:1:1 to receive BNT162b2 at 30 μg , BNT162b2 at 60 μg , BNT162b2 OMI at 30 μg , BNT162b2 OMI at 60 μg , a combination of BNT162b2 and BNT162b2 OMI at 30 μg (15 μg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 μg (30 μg each) at Visit 601 as a fourth dose. Participants 18 to 55 years of age will be randomized to receive bivalent BNT162b2 and BNT162b2 OMI at 60 μg (30 μg each), bivalent BNT162b2 and BNT162b2 OMI at 30 μg (15 μg each), or BNT162b2 OMI at 60 μg at Visit 601 as a fourth dose.

Initially, for participants >55 years of age, sentinel cohorts (sponsor open-label) of 20 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 30 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 90 sentinel-cohort participants. An IRC will review all reported AEs and reactogenicity e-diary data from the sentinel cohorts collected through Day 7 to allow expanded enrollment of an additional 300 participants per group upon confirmation of an acceptable safety assessment. If the safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

For participants 18 to 55 years of age, sentinel cohorts (sponsor open-label) of 30 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 15 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 75 sentinel-cohort participants. An IRC will review all reported AEs, reactogenicity e-diary data, and troponin levels from the sentinel cohorts collected through Day 7 to allow expanded enrollment upon confirmation of an acceptable safety assessment. An additional 900 participants will be enrolled and randomized in a 3:1:2 ratio to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg.

[Table 12](#) and [Table 13](#) describe the enrollment of the sentinel cohorts and steps to progress to expanded enrollment for the >55-year age groups and 18- to 55-year age groups, respectively.

Table 12. Substudy E – Participants >55 Years of Age – Sentinel and Expanded Enrollment

Initial-Sentinel Enrollment ^a		
Group	Study Intervention	Number of Participants
1	BNT162b2 30 µg (participants >55 years of age)	5
2	BNT162b2 60 µg (participants >55 years of age)	5
3	BNT162b2 OMI 30 µg (participants >55 years of age)	5
4	BNT162b2 OMI 60 µg (participants >55 years of age)	5
5	Combination of BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) ^b (participants >55 years of age)	5
6	Combination of BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) ^b (participants >55 years of age)	5
<i>Study team review of Day 1 and Day 2 e-diary reactogenicity data from sentinel-cohort participants</i>		
Expanded-Sentinel Enrollment ^a		
Group	Study Intervention	Number of Participants
1	BNT162b2 30 µg (participants >55 years of age)	15
2	BNT162b2 60 µg (participants >55 years of age)	15
3	BNT162b2 OMI 30 µg (participants >55 years of age)	15
4	BNT162b2 OMI 60 µg (participants >55 years of age)	15
5	Combination of BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) ^b (participants >55 years of age)	15
6	Combination of BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) ^b (participants >55 years of age)	15
<i>IRC review of all reported AE and reactogenicity e-diary data from the sentinel cohorts collected through Day 7. Expanded enrollment to commence upon confirmation of an acceptable safety assessment.</i>		
Expanded Enrollment ^c		
Group	Study Intervention	Number of Participants
1	BNT162b2 30 µg (participants >55 years of age)	300
2	BNT162b2 60 µg (participants >55 years of age)	300
3	BNT162b2 OMI 30 µg (participants >55 years of age)	300
4	BNT162b2 OMI 60 µg (participants >55 years of age)	300
5	Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) ^d (participants >55 years of age)	300
6	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) ^d (participants >55 years of age)	300

Abbreviation: IRC = independent review committee.

- Sentinel cohorts will be sponsor open-label.
- Initial- and expanded-sentinel enrollment participants randomized to combination BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive doses that are prepared at the investigator site from 1 vial each of diluted BNT162b2 vaccine and BNT162b2 OMI vaccine.
- If the IRC's safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).
- Expanded-enrollment participants randomized to bivalent BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive the doses from a single 100-µg/mL vial of BNT162b2 bivalent [Wild Type and Omicron (B.1.1.529)] preformulated vaccine suspension for injection. No dilution is required.

Table 13. Substudy E – Participants 18 to 55 Years of Age – Sentinel and Expanded Enrollment

Initial-Sentinel Enrollment^{a,b}		
Group	Study Intervention	Number of Participants
7	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age)	5
8	Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) (participants 18 to 55 years of age)	5
9	BNT162b2 OMI 60 µg (participants 18 to 55 years of age)	5
<i>Study team review of Day 1 and Day 2 e-diary reactogenicity data from sentinel-cohort participants</i>		
Expanded-Sentinel Enrollment		
Group	Study Intervention	Number of Participants
7	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age)	25
8	Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) (participants 18 to 55 years of age)	25
9	BNT162b2 OMI 60 µg (participants 18 to 55 years of age)	25
<i>IRC review of all reported AE and reactogenicity e-diary data from the sentinel cohorts collected through Day 7. Expanded enrollment to commence upon confirmation of an acceptable safety assessment.</i>		
Expanded Enrollment^c		
Group	Study Intervention	Number of Participants
7	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age)	450
8	Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) (participants 18 to 55 years of age)	150
9	BNT162b2 OMI 60 µg (participants 18 to 55 years of age)	300

Abbreviation: IRC = internal review committee.

- Sentinel cohorts will be sponsor open-label.
- Participants randomized to bivalent BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive the doses from a single 100-µg/mL vial of BNT162b2 bivalent ([Wild Type and Omicron [(B.1.1.529)]] preformulated vaccine suspension for injection. No dilution is required.
- If the IRC's safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

10.11.4.2. Scientific Rationale for Substudy E Design

See [Section 10.11.2.1](#).

10.11.4.2.1. Diversity of Study Population

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

10.11.4.3. Justification for Dose

See [Section 4.3](#) for a justification of the BNT162b2 and BNT162b2 OMI dose used in Substudy E.

10.11.4.4. End of Study Definition

See [Section 4.4](#).

10.11.5. Study Population

Details of the master and Substudy E eligibility criteria are shown in [Section 5](#). Participants must meet all of the general inclusion and exclusion criteria as specified for the master protocol as well as Substudy E-specific inclusion and exclusion criteria.

10.11.5.1. Inclusion Criteria

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

Age and Sex:

1. Groups 1 to 6: Male or female participants >55 years of age

or

Groups 7 to 9: Male or female participants 18 to 55 years of age

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

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in [Section 10.15](#).

Informed Consent:

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

Other Inclusions:

5. Participants who have received 3 prior doses of 30 µg BNT162b2, with the third dose being 5 to 12 months (150 to 360 days) before Visit 601 (Day 1).

Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

6. Groups 7 to 9 (sentinel participants): Screening troponin levels must be within normal range prior to randomization.

10.11.5.2. Exclusion Criteria

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

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
3. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.
4. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
5. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥ 14 days at a dose of ≥ 20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. Prior receipt of any COVID-19 vaccine other than BNT162b2.

Other Exclusions:

10. Investigator site staff or Pfizer-BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
11. Receipt of medications intended to prevent COVID-19.
12. Participation in other studies involving study intervention within 28 days prior to study entry through and including 28 days after the dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

10.11.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy E as detailed in [Section 5.3](#) and [Section 10.4](#).

10.11.5.4. Screen Failures

See [Section 5.4](#).

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

See [Section 5.5](#).

10.11.6. Study Intervention(s) and Concomitant Therapy

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

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg.
- BNT162b2 OMI (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg.
- Combination of BNT162b2 and BNT162b2 OMI (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg (site-prepared dosing suspension from 1 vial each of diluted BNT162b2 and BNT162b2 OMI for the sentinel-cohort participants in Groups 1 to 6, or a preformulated bivalent mixture [no dilution required] in a single vial for the expanded-enrollment participants in Groups 1 to 6 and for all cohorts in Groups 7 to 9).

Note: If the IRC's safety assessment is considered not to be acceptable, then the 60-µg dose levels for BNT162b2, BNT162b2 OMI, and the combination of BNT162b2 and BNT162b2 OMI may be replaced by 50-µg dose levels for the expanded enrollment (combination of BNT162b2 and BNT162b2 OMI at 25 µg each).

10.11.6.1. Study Intervention(s) Administered

Additional Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	Combination BNT162b2 and BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) Site-Prepared Dosing Suspension Using 2 Vials (Dilution Required)	Combination BNT162b2 Bivalent [Wild Type and Omicron (B.1.1.529)] Preformulated as a Single Vial (No Dilution Required)
Type	Vaccine	Vaccine	Vaccine	Vaccine
Dose Formulation	modRNA	modRNA	modRNA	modRNA
Unit Dose Strength(s)	10 µg/0.1 mL	10 µg/0.1 mL	10 µg/0.1 mL	10 µg/0.1 mL
Dosage Level(s)	30-µg or 60-µg ^a	30-µg or 60-µg ^a	30-µg (15-µg each) or 60-µg (30-µg each) ^a	30-µg (15-µg each) or 60-µg (30-µg each) ^a
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Experimental
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor ^b	Provided centrally by the sponsor ^c

Additional Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	Combination BNT162b2 and BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) Site-Prepared Dosing Suspension Using 2 Vials (Dilution Required)	Combination BNT162b2 Bivalent [Wild Type and Omicron (B.1.1.529)] Preformulated as a Single Vial (No Dilution Required)
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement

- If the IRC's safety assessment is considered not to be acceptable, then the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).
- The combination of BNT162b2 and BNT162b2 OMI for the sentinel-cohort participants in Groups 1 to 6 will be a dosing suspension prepared at the investigator site from 1 vial each of diluted BNT162b2 vaccine and BNT162b2 OMI vaccine at the dose levels shown in this table.
- The bivalent formulation of BNT162b2 and BNT162b2 OMI for the expanded-cohort participants in Groups 1 to 6 and for all cohorts in Groups 7 to 9 will be provided as a preformulated suspension for injection in a single vial. No dilution is required.

10.11.6.1.1. Administration

Participants will receive 1 dose of study intervention as allocated by the IRT at Visit 601 in accordance with the substudy's SoA ([Section 10.11.1.3](#)).

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

10.11.6.1.2. Preparation and Dispensing

Study intervention will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way as to ensure that the participants remain blinded.

10.11.6.2. Measures to Minimize Bias: Randomization and Blinding

10.11.6.2.1. Blinding of Site Personnel

Study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

10.11.6.2.2. Blinding of the Sponsor

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

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.
- An unblinded team supporting interactions with, and analyses for, the DMC and IRC (see [Section 10.11.9.4.2](#)). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.
- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.

When a participant has completed their 3-month visit (Visit 604), they may be unblinded to confirm the vaccine and dose received. The study team will also become unblinded to the participant's original study intervention allocation at this time.

10.11.6.2.3. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

10.11.6.3. Study Intervention Compliance

See [Section 6.4](#).

10.11.6.4. Dose Modification

See [Section 6.5](#).

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

See [Section 6.6](#).

10.11.6.6. Treatment of Overdose

See [Section 6.7](#).

10.11.6.7. Concomitant Therapy

See [Section 6.8](#).

10.11.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See [Section 7](#).

10.11.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 250 mL. Sentinel-cohort participants in Groups 7, 8, and 9 will also have 20 mL of blood drawn for troponin measurements. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of up to approximately 855 mL.

For all participants, other 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 60 consecutive days.

10.11.8.1. Surveillance for COVID-19

If, at any time, a participant develops acute respiratory illness (see [Section 10.11.8.6.8](#)), for the purposes of the study, he or she will be considered to potentially have COVID-19 illness. 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 collection of a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid Xpert Xpress SARS-CoV-2; authorized by the FDA under EUA and Pfizer-validated), 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 10.11.8.6.9](#)) 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 as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
 - Fever;
 - New or increased cough;
 - New or increased shortness of breath;
 - Chills;
 - New or increased muscle pain;
 - New loss of taste or smell;
 - Sore throat;
 - Diarrhea;

- Vomiting.
- Confirmed severe COVID-19 (FDA definition⁴⁵): confirmed COVID-19 and presence of at least 1 of the following:
 - Clinical signs at rest indicative of severe systemic illness (RR \geq 30 breaths per minute, HR \geq 125 beats per minute, SpO₂ \leq 93% on room air at sea level, or PaO₂/FiO₂ $<$ 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 definition⁴⁶): 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.

10.11.8.2. Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the [SoA](#). The test to be performed will be the SARS-CoV-2 neutralizing assay (reference strain and Omicron strain). Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory.

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each >55-year age group (Groups 1 to 6) and up to approximately 90 participants across the 18- to 55-year age groups (Groups 7 to 9) during the extended enrollment (no sentinel participants will have this additional blood sample drawn) for isolation of PBMCs. These samples will be used to describe B-cell and T-cell responses to Omicron and the reference strain. A blood sample of ~5 mL for HLA typing will also be obtained.

10.11.8.3. Safety Assessments

See [Section 8.2](#).

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

See [Section 8.3](#).

10.11.8.5. Specified Genetics

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

See [Appendix 16](#) for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

10.11.8.6. Substudy E Procedures

10.11.8.6.1. Screening (0 to 14 Days Before Visit 601) (Only for Sentinel-Cohort Participants 18 to 55 Years of Age in Groups 7, 8, and 9)

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

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.

- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample (approximately 10 mL) for troponin levels.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.11.8.6.9](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

10.11.8.6.2. Visit 601 – Substudy E Vaccination (Day 1)

For Participants >55 Years of Age in Groups 1 to 6 and Expanded-Cohort Participants 18 to 55 Years of Age in Groups 7 to 9:

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the

ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.

For All Participants:

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Record AEs as described in [Section 8.3](#).

- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and fever (COVID-19 surveillance) and provide instructions on their use.
- Explain the e-diary technologies available for this study (see [Section 8.2.4](#)), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
- Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.
- Provide instructions on COVID-19 illness e-diary completion and ask the participant 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 10.11.8.6.8](#) for further details. Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).

- 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 to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.11.8.6.12](#)).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.11.8.6.9](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the reactogenicity e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.11.8.6.3. Visit 601A – 3-Day Follow-Up Visit (2 to 4 Days After Visit 601) (Only for Sentinel-Cohort Participants 18 to 55 Years of Age in Groups 7, 8, and 9)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 5.3](#).

- Collect a blood sample (approximately 10 mL) for troponin levels (only for sentinel-cohort participants 18 to 55 years of age in Groups 7, 8, and 9).
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.11.8.6.12](#)).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.11.8.6.9](#).
- Ensure the participant has a self-swab kit.
- 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.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.11.8.6.4. Visit 602 – 1-Week Follow-Up Visit (6-8 Days After Visit 601)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.11.8.6.12](#)).

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.11.8.6.9](#).
- Ensure the participant has a self-swab kit.
- 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.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.11.8.6.5. Visit 603 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 601)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.11.8.6.9](#).

- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.11.8.6.6. Visit 604 – 3-Month Follow-Up Visit (85 to 95 Days After Visit 601)

- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.11.8.6.9](#).
- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.11.8.6.7. Visit 605 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 601)

- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant 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.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.11.8.6.8. COVID-19 Surveillance (All Substudy E Participants)

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

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

- Diarrhea;
- Vomiting.

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs.

Participants may utilize a COVID-19 illness e-diary through an application (see [Section 10.11.8.6.10](#)) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

10.11.8.6.9. 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, video-conferencing 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:

- Record AEs, as appropriate as described in [Section 8.3](#). Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if the visit is conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship 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 \geq 30 breaths per minute, HR \geq 125 beats per minute, SpO₂ \leq 93% on room air at sea level, or PaO₂/FiO₂ <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 C-reactive protein.
 - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction.
 - Number and type of any healthcare contact; duration of hospitalization and ICU stay.
 - Death.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.11.8.6.10. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant 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 and the study site staff will be established. The participant 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:

- Contact with the investigator, including the ability of the participant to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- If a participant is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

10.11.8.6.11. SARS-CoV-2 NAAT Results

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

- Visit 601: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence of past SARS-CoV-2 infection.
- 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 Visit 601 swab, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

10.11.8.6.12. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably 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.

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

If a Grade 3 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever ([Section 8.2.4.4](#)) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever ([Section 8.2.4.4](#)) 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 recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

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

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

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

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in [Section 8.2.4.2](#).
- Assess systemic events (if present) in accordance with the grades provided in [Section 8.2.4.3](#).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

10.11.9. Statistical Considerations for Substudy E

See [Section 9](#) for master protocol statistical considerations, and see substudy specifics below.

10.11.9.1. Statistical Hypotheses

10.11.9.1.1. Estimands

The estimands corresponding to the primary and exploratory objectives are described in the table in [Section 10.11.3](#).

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

10.11.9.1.2. Statistical Hypotheses

The primary and secondary immunogenicity objectives for participants >55 years of age will be evaluated by the following statistical hypotheses. The immunogenicity objectives for participants 18 through 55 years are descriptive only.

Superiority and Noninferiority of Anti-Omicron Immune Responses

The primary immunogenicity objectives are to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response induced by a dose of BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) relative to the anti-Omicron immune response elicited by a dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age. Each primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

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

where $\ln(2)$ corresponds to a 1-fold superiority criterion and

- $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after 1 dose of BNT162b2 OMI or bivalent BNT162b2 and BNT162b2 OMI given as a fourth dose;
- $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose (Group 1).

- The second null hypothesis (H_0) is

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

where -5% is the noninferiority margin for seroresponse and

- p_1 is the percentage of participants with seroresponse to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI or bivalent BNT162b2 and BNT162b2 OMI given as a fourth dose;
- p_2 is the percentage of participants with seroresponse to the Omicron strain at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose (Group 1).

Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times \text{LLOQ}$ is considered seroresponse.

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

The secondary objective of “super” superiority will be evaluated using a 1.5-fold margin for GMR. “Super” superiority for GMR will be established if the lower limit of the 2-sided 95% CI for the GMR is greater than 1.5.

Noninferiority of Anti–Reference Strain Immune Responses

The noninferiority immunogenicity objectives on anti–reference strain immune responses are to assess the noninferiority of the anti–reference strain immune response induced by a dose of bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) relative to the anti–reference strain immune response elicited by a dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age. Each noninferiority objective will be evaluated by the following hypothesis:

- The null hypothesis (H_0) is

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

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

- $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose (Group 5 or Group 6);
- $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured 1 month after 1 dose of BNT162b2 given as a fourth dose (Group 1).

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

10.11.9.1.3. Multiplicity Adjustment

The primary and secondary immunogenicity objectives for participants >55 years of age will be assessed using the expanded-enrollment cohort.

The primary and secondary immunogenicity objectives for participants >55 years of age will be evaluated in sequential order as listed below using a 1-sided alpha of 0.025:

- Superiority in GMR and noninferiority in seroresponse rate for Omicron response: G4vG1A (OMI-60) → G6vG1A (bivalent-60) → G5vG1A (bivalent-30) →
- Noninferiority in GMR for reference strain response: G6vG1B (bivalent-60) → G5vG1B (bivalent-30) →
- “Super” superiority in GMR for Omicron response: G4vG1B (OMI-60) → G6vG1C (bivalent-60) → G5vG1C (bivalent-30) →
- Superiority in GMR and noninferiority in seroresponse rate for Omicron response: G3vG1A (OMI-30) → G3vG1B (OMI-30)

For objectives involving 2 hypotheses, hypotheses based on GMR and seroresponse rate difference will be assessed sequentially in the order as stated. Both hypotheses within the objective must be established before assessing the next objective in the sequence. Therefore, the overall type I error is fully controlled.

The immunogenicity objectives for participants 18 through 55 years of age are descriptive only; therefore, no multiplicity adjustment is applied.

10.11.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized or assigned, have a 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 randomized/assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

10.11.9.3. Statistical Analyses

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

10.11.9.3.1. General Considerations

All analyses will be performed separately for each age group (18-55 years of age, >55 years of age).

Refer to [Section 9.3.1](#) for general considerations of statistical analyses.

A sensitivity analysis of GMR and difference in seroresponse rate for between-group comparison may be performed. The GMR and associated 95% CI will be calculated by exponentiating the difference in least-squares means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model with terms of baseline assay results (log scale) and vaccine group. The difference in seroresponse rate between 2 vaccine groups and the associated 95% CI will be calculated using the stratified Miettinen and Nurminen method adjusting for the corresponding baseline assay result category (< median, \geq median).

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

Endpoint	Statistical Analysis Methods
Safety	<p>For each age group (18-55 years of age, >55 years of age):</p> <ul style="list-style-type: none"> Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Local reactions and systemic events from Day 1 through Day 7 after the study vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after study vaccination will be provided for each vaccine group. <p>For sentinel-cohort participants 18 to 55 years of age:</p> <ul style="list-style-type: none"> Counts and percentages of participants with elevated troponin I levels before and 3 days after study vaccination, and associated Clopper-Pearson 95% CIs, will be provided for each vaccine group.
Immunogenicity	<p>For each primary immunogenicity estimand described in Section 10.11.3,</p> <ul style="list-style-type: none"> GMRs and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.2.3. The percentages of participants with seroresponse for each group will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method (see Section 9.3.1.1). Only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection will be included in the analysis. Superiority based on GMR will be established if the lower bound of the 2-sided 95% CI for the GMR is >1. Noninferiority based on seroresponse rate difference will be established if the lower bound of the 2-sided 95% CI for the difference in percentage is greater than -5%. GMRs and the associated 2-sided 95% CI, and the difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs, may be estimated using the sensitivity analysis approach specified in Section 10.11.9.3.1.

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

Endpoint	Statistical Analysis Methods
Immunogenicity	<p>For each secondary immunogenicity estimand described in Section 10.11.3.</p> <ul style="list-style-type: none"> GMR and the associated 2-sided 95% CIs will be calculated using the same method as for the primary immunogenicity objectives. Noninferiority of anti-reference strain immune response based on the GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥ 0.8. “Super” superiority of anti-Omicron immune response will be established if the lower bound of the 2-sided 95% CI for the GMR is >1.5. GMRs and the associated 2-sided 95% CI may be estimated using the sensitivity analysis approach specified in Section 10.11.9.3.1.

10.11.9.3.4. Exploratory Endpoint(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	<p>GMTs and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers</p> <p>Percentages of participants with seroresponse to Omicron- or reference-strain</p> <p>For each age group (18-55 years of age, >55 years of age):</p> <ul style="list-style-type: none"> GMTs at each time point and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers from before the study vaccination to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group using the statistical method described in Section 9.3.1.2.1 and Section 9.3.1.2.2. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group.

Endpoint	Statistical Analysis Methods
	<ul style="list-style-type: none"> GMRs and the differences in percentages of participants with seroresponse between certain vaccine groups of interest may be calculated along with the associated 2-sided 95% CIs. <p>GMTs and GMFRs of SARS-CoV-2 reference-strain– and VOC-neutralizing titers for participants in the sentinel cohorts</p> <p>For each age group (18-55 years of age, >55 years of age):</p> <ul style="list-style-type: none"> GMTs at each time point and GMFRs of SARS-CoV-2 reference-strain– and VOC-neutralizing titers from before the study vaccination to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group for sentinel cohorts. <p>GMTs for any VOCs not already specified</p> <p>For each age group (18-55 years of age, >55 years of age):</p> <ul style="list-style-type: none"> GMTs of reference-strain or VOC-neutralizing titers, along with the associated 2-sided 95% CIs, will be provided at specific time points for each group. GMFRs and GMRs of VOC-neutralizing titers to reference-strain–neutralizing titers may also be calculated along with the associated 2-sided 95% CIs.
COVID-19 cases	Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized for each age group.
Cell-mediated immune response	The cell-mediated immune response and additional humoral immune response parameters to the reference strain and Omicron will be summarized at each time point for the subset of participants with PBMC samples collected in each vaccine group for each age group.

10.11.9.4. Interim Analyses

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

10.11.9.4.1. Analysis Timing

Statistical analyses will be carried out when the following data are available for each age group:

- Safety data through 1 month after study vaccination for each group in the sentinel cohorts.
- Immunogenicity data through 1 month after study vaccination for each group in the sentinel cohorts.
- Safety data through 1 month after study vaccination for each group in the expanded-enrollment cohort.
- Immunogenicity data through 1 month after study vaccination for each group in the expanded-enrollment cohort.
- Complete safety and immunogenicity analysis approximately 6 months after study vaccination for each group in the sentinel or expanded-enrollment cohorts.

Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses for the expanded-enrollment cohort conducted while the study is ongoing will be performed by an unblinded team.

10.11.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC and DMC. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only for the sentinel cohort and will include:

- Review of all reported AEs, e-diary reactogenicity data, and troponin levels collected through Day 7 from all sentinel-cohort participants. This safety assessment will be conducted to determine if the study team may proceed with expanded enrollment of approximately 300 participants per group.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter.

The recommendations made by the DMC will be forwarded to the appropriate 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.

10.11.9.5. Sample Size Determination

The sample size in each group is based on consideration of an acceptable safety database. For the >55-year age group, a random sample of 230 participants will be selected from each group in the expanded-enrollment cohort as an immunogenicity subset to evaluate the primary and secondary immunogenicity objectives. Assuming a 35% nonevaluable or prior infection rate, approximately 150 evaluable participants in each group will contribute to the primary immunogenicity evaluation.

Superiority and Noninferiority of Anti-Omicron Immunogenicity Objectives

For comparisons based on GMR, assuming common assay standard deviations of 1.05 in log scale based on data observed in the Phase 2 part of the C4591001 study for participants 56 years of age or older and adjusted for assay variability, if the true GMR is 1.5, with 150 evaluable participants, the study will have 91.5% power to demonstrate superiority. If the true GMR is 2.0, the study will have 65.7% power to declare “super” superiority using a 1.5-fold margin.

For comparisons based on seroresponse rate difference, if the seroresponse rate is 70% in the BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) group and 55% in the BNT162b2 30 µg group, the study will have 94.9% power to demonstrate noninferiority using a 5% margin.

Noninferiority of Anti-Reference Strain Immunogenicity Objectives

For comparisons based on GMR, common assay standard deviations of 1.05 and a GMR of 1 are assumed for each comparison. With 150 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has 90.9% power to demonstrate noninferiority based on the GMR using a 1.5-fold margin.

For safety outcomes, Table 14 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 1%, with 300 participants in a vaccine group, there is 95% probability of observing at least 1 AE.

Table 14. Substudy E – Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=20	N=300	N=900	N=1920
0.01%	0.002	0.03	0.09	0.17
0.02%	0.004	0.06	0.16	0.32
0.05%	0.01	0.14	0.36	0.62
0.10%	0.02	0.26	0.59	0.85
0.20%	0.04	0.45	0.84	0.98
0.50%	0.10	0.78	0.99	>0.99
1.00%	0.18	0.95	>0.99	>0.99
2.00%	0.33	>0.99	>0.99	>0.99

Table 14. Substudy E – Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=20	N=300	N=900	N=1920
5.00%	0.64	>0.99	>0.99	>0.99
10.0%	0.88	>0.99	>0.99	>0.99

10.12. Appendix 12: Substudy F

10.12.1. Substudy Summary

10.12.1.1. Substudy Synopsis

See [Section 1.1](#) for a synopsis of Substudy F.

10.12.1.2. Schema

Visit Number	701	702	703	704	705
Visit Description	4 th Dose of BNT162b2 or BNT162b2 OMI or Combination BNT162b2/BNT162b2 OMI	7 Days After 4 th Vaccination	1 Month After 4 th Vaccination	3 Months After 4 th Vaccination	6 Months After 4 th Vaccination
Participants having received 3 prior doses of 30 µg BNT162b2 ≥4 months prior to randomization	30-µg OR 60-µg dose				
Blood draw for immunogenicity assessments ^a	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL
Blood draw for additional laboratory testing ^b	~35 mL	~35 mL	~35 mL	~35 mL	~35 mL

a. ~11 mL for Pfizer central laboratory testing, ~11 mL for Sheba laboratory testing, and ~3 mL for BioNTech laboratory testing. See [Section 10.12.8.2](#).

b. ~35 mL collected for PBMC for Sheba and BioNTech as described in [Section 10.12.8.2](#).

10.12.1.3. Schedule of Activities for Substudy F

Visit Number	701	702	703	704	705	Unplanned
Visit Description	Vaccination	1-Week Follow-Up Visit After Vaccination	1-Month Follow-Up Visit After Vaccination	3-Month Follow-Up Visit After Vaccination	6-Month Follow-Up Visit After Vaccination	Potential COVID-19 Illness Visit ^a
Visit Window (Days)	Day 1 ^b	6 to 8 Days After Visit 701	28 to 35 Days After Visit 701	85 to 95 Days After Visit 701	175 to 189 Days After Visit 701	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Obtain informed consent	X					
Perform SARS-CoV-2 antigen test	X					
Assign participant number	X					
Obtain demography and medical history data	X					
Perform clinical assessment ^c	X					
Measure height and weight	X					
Measure temperature (body)	X					
Perform urine pregnancy test (if appropriate)	X					
Confirm use of contraceptives (if appropriate)	X	X	X			
Collect nonstudy vaccine information	X	X	X	X	X	
Collect prohibited medication use		X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	
Confirm eligibility	X					
Review temporary delay criteria	X					
Collect blood sample for immunogenicity assessments ^d	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL	
Collect blood sample for additional laboratory testing ^e	~35 mL	~35 mL	~35 mL	~35 mL	~35 mL	
Obtain nasal (midturbinate) swab	X					X
Obtain the participant's vaccine vial allocation using the IRT system	X					
Administer study intervention	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X					

Visit Number	701	702	703	704	705	Unplanned
Visit Description	Vaccination	1-Week Follow-Up Visit After Vaccination	1-Month Follow-Up Visit After Vaccination	3-Month Follow-Up Visit After Vaccination	6-Month Follow-Up Visit After Vaccination	Potential COVID-19 Illness Visit ^a
Visit Window (Days)	Day 1 ^b	6 to 8 Days After Visit 701	28 to 35 Days After Visit 701	85 to 95 Days After Visit 701	175 to 189 Days After Visit 701	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X					
Provide/ensure the participant has a thermometer and measuring device	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	X→	X→				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X			
Collect AEs and SAEs as appropriate	X	X	X ^f	X ^f	X ^f	X
Collect e-diary or assist the participant to delete application					X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs	X	X	X	X		

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.

- The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
- The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
- Including, if indicated, a physical examination.
- ~11 mL for Pfizer central laboratory testing, ~11 mL for Sheba laboratory testing, and ~3 mL for BioNTech laboratory testing. See [Section 10.12.8.2](#).
- ~35 mL collected for PBMC for Sheba and BioNTech as described in [Section 10.12.8.2](#).
- Any AEs occurring up to 48 hours after the blood draw must be recorded (see [Section 8.3.1](#)).

10.12.2. Introduction

10.12.2.1. Study Rationale

The SARS-CoV-2 variant B.1.1.529, also known as Omicron, is currently the dominant variant in many countries and within the US is responsible for 98.3% of sequenced COVID-19 cases as of 08 January 2022.²⁵ Current data note that the vaccine effectiveness against hospitalization is 88% (78%-93%) for Omicron after 3 doses of vaccine.²⁶ However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant. The addition of a higher-dose booster may improve protection, particularly in older individuals, with increased longevity of an immune response, provided it has a tolerable safety profile.²⁷ Therefore, Substudy F has been designed to evaluate high-dose BNT162b2 OMI (60 µg), high-dose BNT162b2 (60 µg), and a high-dose combination of BNT162b2 OMI and BNT162b2 (30 µg of each), compared to BNT162b2 OMI 30 µg, BNT162b2 30 µg, and a combination of BNT162b2 OMI and BNT162b2 (15 µg of each), given as a fourth dose.

See [Section 2.2](#) for the study background.

10.12.2.2. Benefit/Risk Assessment

A tolerability profile of a 60-µg dose of BNT162b2 has yet to be established. However, BNT162b1 (a candidate RNA-LNP vaccine tested in clinical trial C4591001 utilizing nucleoside-modified messenger RNA similar to BNT162b2 but instead of encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein, BNT162b1 encodes the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain) was studied in adults 18 to 55 years of age at dose levels of 50 µg, 60 µg, and 100 µg. In one study, 60 participants were vaccinated with BNT162b1. Twelve participants for each of the dose level groups (1 µg, 10 µg, 30 µg, 50 µg, and 60 µg) were to receive the first dose on Day 1 and a second dose on Day 22. Due to the tolerability observed in participants after 2 doses of 50 µg and after reviewing the totality of the data available, including the local and systemic reactogenicity data, such as the increasing number of severe (Grade 3) systemic reactions reported with ascending dose, a second dose of 60 µg was not administered.^{37,47} Another study investigated BNT162b1 at 10 µg, 30 µg, and 100 µg. Participants in this study were not administered the second dose of 100 µg because of the increased reactogenicity profile seen after a single dose at 100 µg and in participants who received 2 doses of 30 µg.³⁸ In light of better tolerability of BNT162b2 (compared to BNT162b1), and better tolerability in older adults (compared to younger adults), the potential benefit of a 60-µg dose of BNT162b2 is likely to outweigh the risk.

10.12.2.2.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy F may be:

- Receipt of a fourth dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic, particularly against new variant-associated infection and disease.

- Contributing to research to help others in a time of global pandemic.

10.12.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety		
<ul style="list-style-type: none"> To describe the safety and tolerability profile of BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and a combination of BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants 	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Local reactions (pain at the injection site, redness, and swelling) Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) AEs SAEs
Primary Immunogenicity		
To describe the immune response to BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and a combination of BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose in BNT162b2-experienced participants	<ul style="list-style-type: none"> GMT at each time point GMFRs from before the study vaccination to subsequent time points Percentages of participants with seroresponse^a at each time point GMRs at each time point after the study vaccination between different vaccine groups 	<ul style="list-style-type: none"> SARS-CoV-2 Omicron-neutralizing titers SARS-CoV-2 reference-strain-neutralizing titers
<ul style="list-style-type: none"> Exploratory 		
To describe the immune response to any VOCs not already specified		<ul style="list-style-type: none"> SARS-CoV-2 neutralizing titers for any VOCs not already specified
To describe the cell-mediated immune response and additional immune response parameters		<ul style="list-style-type: none"> T-cell (by ELISPOT) and B-cell characterization RBD binding IgG RBD binding IgA
To describe confirmed COVID-19 and severe COVID-19 cases		<ul style="list-style-type: none"> Confirmed COVID-19 cases Confirmed severe COVID-19 cases Strain sequencing of COVID-19 cases

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

10.12.4. Study Design

10.12.4.1. Overall Design

This is a randomized, observer-blinded substudy to describe the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 OMI (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), given as a single dose. Approximately 180 participants ≥ 60 years of age who have received 3 prior

doses of BNT162b2 (30 µg doses) with the most recent dose being ≥ 4 months prior to randomization, will be enrolled in Israel. Participants will be randomized at a ratio of 1:1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 OMI at 30 µg, BNT162b2 OMI at 60 µg, a combination of BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each) at Visit 701 as a fourth dose.

Initially, sentinel cohorts (sponsor open-label) of 5 participants per group will be enrolled. An IRC and site representatives will review all reported AEs and reactogenicity e-diary data from the sentinel cohorts collected through Day 7 to allow expanded enrollment of an additional 25 participants per group upon confirmation of an acceptable safety assessment. If the safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

Table 15 describes the enrollment of the sentinel cohorts and steps to progress to expanded enrollment.

Table 15. Substudy F – Sentinel and Expanded Enrollment

Sentinel Enrollment ^a	
Study Intervention	Number of Participants
BNT162b2 30 µg	5
BNT162b2 60 µg	5
BNT162b2 OMI 30 µg	5
BNT162b2 OMI 60 µg	5
Combination of BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)	5
Combination of BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)	5
<i>IRC and site representatives' review of all reported AE and reactogenicity e-diary data from the sentinel cohorts collected through Day 7. Expanded enrollment to commence upon confirmation of an acceptable safety assessment.</i>	
Expanded Enrollment ^b	
Study Intervention	Number of Participants
BNT162b2 30 µg	25
BNT162b2 60 µg	25
BNT162b2 OMI 30 µg	25
BNT162b2 OMI 60 µg	25
Combination of BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)	25
Combination of BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)	25

a. Sentinel cohorts will be sponsor open-label.

b. If the IRC and site representative's safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

10.12.4.2. Scientific Rationale for Substudy F Design

See [Section 10.12.2.1](#).

10.12.4.3. Justification for Dose

See [Section 4.3](#) for a justification of the BNT162b2 and BNT162b2 OMI dose used in Substudy F.

10.12.4.4. End of Study Definition

See [Section 4.4](#).

10.12.5. Study Population

Details of the master eligibility criteria are shown in [Section 5](#). Substudy F-specific eligibility criteria are listed in Sections 10.12.5.1 and [10.12.5.2](#).

10.12.5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants ≥ 60 years of age:

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

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in [Section 10.15](#).

Informed Consent:

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

Other Inclusions:

5. Participants who have received 3 prior doses of 30 μg BNT162b2, with the third dose being ≥ 4 months before Visit 701 (Day 1).

Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

10.12.5.2. Exclusion Criteria

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

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
3. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19 or positive antigen test for SARS-CoV-2 at baseline.
4. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
5. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥ 14 days at a dose of ≥ 20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. Prior receipt of any COVID-19 vaccine other than BNT162b2.

Other Exclusions:

10. Investigator site staff or Pfizer-BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
11. Receipt of medications intended to prevent COVID-19.
12. Participation in other studies involving study intervention within 28 days prior to study entry through and including 28 days after the dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID-19, which are prohibited throughout study participation.

10.12.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy F as detailed in [Section 5.3](#) and [Section 10.4](#).

10.12.5.4. Screen Failures

See [Section 5.4](#).

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

See [Section 5.5](#).

10.12.6. Study Intervention(s) and Concomitant Therapy

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

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg.
- BNT162b2 OMI (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg.
- Combination of BNT162b2 and BNT162b2 OMI (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg.

Note: If the IRC and site representative's safety assessment is considered not to be acceptable, then the 60-µg dose levels for BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI may be replaced by 50-µg dose levels for the expanded enrollment (combination of BNT162b2 and BNT162b2 OMI at 25 µg each).

10.12.6.1. Study Intervention(s) Administered

Additional Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	Combination BNT162b2 and BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) Site-Prepared Dosing Suspension Using 2 Vials (Dilution Required)
Type	Vaccine	Vaccine	Vaccine
Dose Formulation	modRNA	modRNA	modRNA
Unit Dose Strength(s)	10 µg/0.1 mL	10 µg/0.1 mL	10 µg/0.1 mL
Dosage Level(s)	30-µg or 60-µg ^a	30-µg or 60-µg ^a	30-µg (15-µg each) or 60-µg (30-µg each) ^a
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor ^b
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement

- If the IRC's safety assessment is considered not to be acceptable, then the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).
- The combination of BNT162b2 and BNT162b2 OMI will be dosing suspension prepared at the investigator site from 1 vial each of diluted BNT162b2 Vaccine and BNT162b2 OMICRON (B.1.1.529) at the dose levels shown in this table.

10.12.6.1.1. Administration

Participants will receive 1 dose of study intervention as allocated by the IRT at Visit 701 in accordance with the substudy's SoA ([Section 10.12.1.3](#)).

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

10.12.6.1.2. Preparation and Dispensing

Study intervention will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way as to ensure that the participants remain blinded.

10.12.6.2. Measures to Minimize Bias: Randomization and Blinding

10.12.6.2.1. Blinding of Site Personnel

Study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. However, site personnel, separate from the site study team, that will review safety data with the IRC will be unblinded to the study intervention allocation for the sentinel cohort.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

10.12.6.2.2. Blinding of the Sponsor

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

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.
- An unblinded team supporting interactions with, and analyses for, the DMC and IRC (see [Section 10.12.9.4.2](#)). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.

When a participant has completed their 3-month visit (Visit 704), they may be unblinded to confirm the vaccine and dose received. The study team will also become unblinded to the participant's original study intervention allocation at this time.

10.12.6.2.3. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

10.12.6.3. Study Intervention Compliance

See [Section 6.4](#).

10.12.6.4. Dose Modification

See [Section 6.5](#).

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

See [Section 6.6](#).

10.12.6.6. Treatment of Overdose

See [Section 6.7](#).

10.12.6.7. Concomitant Therapy

See [Section 6.8](#).

10.12.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See [Section 7](#).

10.12.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 300 mL. For all participants, other 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 60 consecutive days.

10.12.8.1. Surveillance for COVID-19

If, at any time, a participant develops acute respiratory illness (see [Section 10.12.8.5.6](#)), for the purposes of the study he or she will be considered to potentially have COVID-19 illness. 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 collection of a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid Xpert Xpress SARS-CoV-2; authorized by the FDA under EUA and Pfizer-validated), 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 10.12.8.5.7](#)) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

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

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

- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.
- Confirmed severe COVID-19 (FDA definition⁴⁵): confirmed COVID-19 and presence of at least 1 of the following:
 - Clinical signs at rest indicative of severe systemic illness (RR \geq 30 breaths per minute, HR \geq 125 beats per minute, SpO₂ \leq 93% on room air at sea level, or PaO₂/FiO₂ $<$ 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 definition⁴⁶): 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.

10.12.8.2. Immunogenicity

Blood samples (~11 mL for Pfizer, ~11 mL for Sheba, and ~3 mL for BioNTech) for serum collection will be obtained for immunogenicity testing at each visit as specified in the [SoA](#). The tests to be performed will be the SARS-CoV-2 neutralizing assays (reference strain and Omicron strain).

Additional whole blood samples (~20 mL for Sheba and ~15 mL for BioNTech) will be collected for PBMC isolation at each visit as specified in the [SoA](#). The testing priority will be ~5 mL for T-cell analysis for Sheba, ~15 mL for B-cell analysis for BioNTech, and ~15 mL for B-cell analysis for Sheba.

10.12.8.3. Safety Assessments

See [Section 8.2](#).

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

See [Section 8.3](#).

10.12.8.5. Substudy F Procedures

10.12.8.5.1. Visit 701 – Substudy F Vaccination (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Perform a SARS-CoV-2 antigen test and confirm that the participant is negative. Record the result in the source documents only.
- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.5](#).
- Discuss contraceptive use as described in [Section 5.3](#).
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity assessments.
- Collect a whole blood sample for additional laboratory testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and fever (COVID-19 surveillance) and provide instructions on their use.

- Explain the e-diary technologies available for this study (see [Section 8.2.4](#)), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required.
- Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.
- Provide instructions on COVID-19 illness e-diary completion and ask the participant 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 10.12.8.5.6](#) for further details. Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - 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 to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.12.8.5.10](#)).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.12.8.5.7](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the reactogenicity e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

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

10.12.8.5.2. Visit 702 – 1-Week Follow-Up Visit (6-8 Days After Visit 701)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity assessments.
- Collect a whole blood sample for additional laboratory testing.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 10.12.8.5.10](#)).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.12.8.5.7](#).
- Ensure the participant has a self-swab kit.
- 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.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

10.12.8.5.3. Visit 703 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 701)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in [Section 5.3](#).
- Collect a blood sample for immunogenicity assessments.
- Collect a whole blood sample for additional laboratory testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 10.12.8.5.7](#).
- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.12.8.5.4. Visit 704 – 3-Month Follow-Up Visit (85 to 95 Days After Visit 701)

- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity assessments.
- Collect a whole blood sample for additional laboratory testing.
- Record nonstudy vaccinations as described in [Section 6.8](#).

- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 10.12.8.5.7](#).
- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.12.8.5.5. Visit 705 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 701)

- Record AEs as described in [Section 8.3](#).
- Collect a blood sample for immunogenicity assessments.
- Collect a whole blood sample for additional laboratory testing.
- Record nonstudy vaccinations as described in [Section 6.8](#).
- Record details of any of the prohibited medications specified in [Section 6.8.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect the participant's e-diary or assist the participant 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.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

10.12.8.5.6. COVID-19 Surveillance (All Substudy F Participants)

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

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

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs.

Participants may utilize a COVID-19 illness e-diary through an application (see [Section 10.12.8.5.8](#)) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

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

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant 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:

- Record AEs, as appropriate as described in [Section 8.3](#). Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in [Section 6.8](#) received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if the visit is conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship 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 \geq 30 breaths per minute, HR \geq 125 beats per minute, SpO₂ \leq 93% on room air at sea level, or PaO₂/FiO₂ <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 C-reactive protein.
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction.
- Number and type of any healthcare contact; duration of hospitalization and ICU stay.
- Death.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.12.8.5.8. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant 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 and the study site staff will be established. The participant 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:

- Contact with the investigator, including the ability of the participant to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- If a participant is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

10.12.8.5.9. SARS-CoV-2 NAAT Results

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

- Visit 701: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence of past SARS-CoV-2 infection.
- 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 Visit 701 swab, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

10.12.8.5.10. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably 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.

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

If a Grade 3 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever ([Section 8.2.4.4](#)) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever

([Section 8.2.4.4](#)) 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 recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

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

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

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

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in [Section 8.2.4.2](#).
- Assess systemic events (if present) in accordance with the grades provided in [Section 8.2.4.3](#).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

10.12.9. Statistical Considerations for Substudy F

See [Section 9](#) for master protocol statistical considerations, and see substudy specifics below.

10.12.9.1. Statistical Hypotheses

10.12.9.1.1. Estimands

The estimands corresponding to the primary and exploratory objectives are described in the table in [Section 10.12.3](#).

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

10.12.9.1.2. Statistical Hypotheses

All objectives in this substudy are descriptive. No hypothesis testing is planned.

10.12.9.1.3. Multiplicity Adjustment

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

10.12.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized or assigned, have a 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 randomized/assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

10.12.9.3. Statistical Analyses

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

10.12.9.3.1. General Considerations

Refer to [Section 9.3.1](#) for general considerations of statistical analyses.

Adjusted Comparison of Antibody Levels

The relative difference in antibody levels between different vaccine groups, using the BNT162b2 30-µg group as the reference, will be estimated using an ANCOVA model. For each time point after the baseline, log-antibody levels will be modeled using a linear regression with the vaccine group as the exposure and the baseline antibody levels as a covariate. The GMR and associated 95% CI will be calculated by exponentiating the difference in least-squares mean and the corresponding CIs.

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

Endpoint	Statistical Analysis Methods
Safety	<ul style="list-style-type: none"> Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Local reactions and systemic events from Day 1 through Day 7 after the study vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after study vaccination will be provided for each vaccine group.
Immunogenicity	<p>GMTs and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers</p> <p>Percentages of participants with seroresponse to Omicron- or reference-strain</p> <p>GMRs between different vaccine groups</p> <ul style="list-style-type: none"> GMTs at each time point and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers from before the study vaccination to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group using the statistical method described in Section 9.3.1.2.1 and Section 9.3.1.2.2.

Endpoint	Statistical Analysis Methods
	<ul style="list-style-type: none"> The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group. Model-based GMRs at each time point after the study vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group (using the BNT162b2 30-μg group as the reference) using the statistical method described in Section 10.12.9.3.1

10.12.9.3.3. Exploratory Endpoint(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	<p>GMTs and GMFRs for any VOCs not already specified</p> <p>GMTs of reference-strain– or VOC-neutralizing titers and GMFRs from before the study vaccination to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided at specific time points for each group.</p> <p>Model-based GMRs of neutralizing titers for VOCs not already analyzed as a primary outcome at a specific time point after the study vaccination, along with the associated 2-sided 95% CIs, may be provided for each vaccine group (using the BNT162b2 30-μg group as the reference) using the statistical method described in Section 10.12.9.3.1.</p> <p>Cell-mediated immune response and additional immune response parameters</p> <p>The cell-mediated immune response and additional immune response parameters will be summarized at each time point.</p>
COVID-19 cases	Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized using the statistical method described in Section 9.3.1.1 .

10.12.9.4. Interim Analyses

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

10.12.9.4.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Safety data through 1 month after study vaccination for each group.
- Immunogenicity data through 1 month after study vaccination for each group.
- Safety and immunogenicity data through 3 months after study vaccination for each group.
- Complete safety and immunogenicity analysis approximately 6 months after study vaccination for each group.

Certain analyses may be combined into a single regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses for the expanded-enrollment cohort conducted while the study is ongoing will be performed by an unblinded team.

10.12.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC and DMC. The IRC is independent of the study team and includes internal members and site representatives. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC and site representatives are only for the sentinel cohort and will include:

- Review of all reported AE and e-diary reactogenicity data collected through Day 7 from all sentinel-cohort participants. This safety assessment will be conducted to determine if the study team may proceed with expanded enrollment of approximately 25 additional participants per group.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter.

The recommendations made by the DMC will be forwarded to the appropriate 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.

10.12.9.5. Sample Size Determination

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

[Table 16](#) shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 1%, with 30 participants in a vaccine group, there is 26% probability of observing at least 1 AE.

Table 16. Substudy F - Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=30	N=90	N=180
0.01%	0.003	0.01	0.02
0.02%	0.006	0.02	0.04
0.05%	0.01	0.04	0.09
0.10%	0.03	0.09	0.16
0.20%	0.06	0.16	0.30
0.50%	0.14	0.36	0.59
1.00%	0.26	0.60	0.84
2.00%	0.45	0.84	0.97
5.00%	0.79	0.99	>0.99
10.0%	0.96	>0.99	>0.99

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 11 (20 Sep 2022)

Overall Rationale for the Amendment:

As part of protocol amendment 11, progression beyond the 12 through 17 years age group in Substudy C will not occur and no further participants will be enrolled. Active participants at the time of this amendment will also only be followed for 6 months after their last study vaccination. Their final visit will be V304.

Active participants in Cohort 1 and Cohort 2 in Substudy D at the time of protocol amendment 11 will also only be followed for 6 months after their last study vaccination, the protocol-specified safety reporting period. Their final visit will be V405.

The endpoints and statistical considerations were updated for Substudy F to further clarify the testing and analyses.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Synopsis – Substudy C Design	Confirmation that progression beyond the 12 through 17 years age group in Substudy C will not occur and no further participants will be enrolled	A third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time and, for Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine, making age escalation operationally unfeasible.	Substantial
Synopsis – Substudy D Design	Confirmed that participants in Cohort 1 and Cohort 2 will only be followed for 6 months after their last study vaccination	The safety follow-up period is 6 months after the last dose; therefore, a longer study duration is not required.	Substantial
Synopsis – Number of Participants (Substudy C)	Confirmed up to 150 participants will be enrolled	Progression beyond the 12 through 17 years age group will not occur.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Synopsis – DMC	Clarified that DMC will only review safety and immunogenicity data in the first approximately 100 participants 7 days after the third dose	Progression beyond the 12 through 17 years age group will not occur.	Substantial
Section 10.8.2.3.1 Benefit Assessment	Updated to include reference to a fourth dose	Protocol clarification.	Nonsubstantial
Section 10.9.1.2 Schema (Substudy C)	Removed the 12-month follow-up visit and the 20-mL blood sample for participants ≥ 18 years of age	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.9.1.3 Schedule of Activities (Substudy C)	Removed the 12-month follow-up visit and the 20-mL blood sample for participants ≥ 18 years of age	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.9.2.1 Study Rationale (Substudy C)	Confirmation that progression beyond the 12 through 17 years age group in Substudy C will not occur, and that the final visit will be 6 months after the last dose	A third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time and, for Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine, making age escalation operationally unfeasible. The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.9.3 Objectives, Estimands, and Endpoints (Substudy C)	Updated objectives in response to change in study design	A third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time and, for Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine, making age escalation operationally unfeasible.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.9.4.1 Overall Design (Substudy C)	Confirmation that progression beyond the 12 through 17 years age group in Substudy C will not occur, and no further subjects will be enrolled	A third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time and, for Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine, making age escalation operationally unfeasible. The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.9.4.1 Overall Design (Substudy C)	Removed reference to blood sample collection at the 12-month visit	Due to decreased study duration.	Substantial
Section 10.9.8 Study Assessments and Procedures (Substudy C)	Clarified total blood sampling volume	The volume reduced as progression beyond the 12 through 17 years age group will not occur, and the 12-month visit was removed.	Substantial
Section 10.9.8.4.1 Visit 301 (Substudy C)	Amended blood sample wording	Progression beyond the 12 through 17 years age group will not occur.	Substantial
Section 10.9.8.4.2 Visit 302 (Substudy C)	Amended blood sample wording	Progression beyond the 12 through 17 years age group will not occur.	Substantial
Section 10.9.8.4.3 Visit 303 (Substudy C)	Amended blood sample wording	Progression beyond the 12 through 17 years age group will not occur.	Substantial
Section 10.9.8.4.4 Visit 304 (Substudy C)	Clarified for participants that have already completed V304 at the time of protocol amendment 11 that they will be informed by the investigator site staff of study completion	Due to removal of the 12-month follow-up visit.	Substantial
Section 10.9.8.4.4 Visit 304 (Substudy C)	Amended blood sample wording	Progression beyond the 12 through 17 years age group will not occur.	Substantial
Section 10.9.8.4.5 Visit 305 (Substudy C)	12-month follow-up visit removed	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.9.9.1.2 Statistical Hypotheses (Substudy C)	Clarified there is no formal hypotheses testing	Due to change in overall substudy design.	Substantial
Section 10.9.9.1.3 Multiplicity Adjustment (Substudy C)	Clarified no multiplicity adjustment is needed for the study	Due to change in overall substudy design.	Substantial
Section 10.9.9.3.2 Primary Endpoint(s)/Estimand(s) Analysis (Substudy C)	Updated objectives in response to change in study design	A third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time and, for Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine, making age escalation operationally unfeasible.	Substantial
Section 10.9.9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis (Substudy C)	Updated objectives in response to change in study design	A third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time and, for Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine, making age escalation operationally unfeasible.	Substantial
Section 10.9.9.3.4 Exploratory Endpoint(s) Analysis (Substudy C)	Updated objective in response to change in study design	A third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time and, for Fall 2022, the recommended booster vaccine will switch to a bivalent original/Omicron-modified vaccine, making age escalation operationally unfeasible.	Substantial
Section 10.9.9.4 Interim Analyses (Substudy C)	Confirmed the administrative interim analysis for 12 through 17 years of age was completed	Protocol clarification.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.9.9.4.1 Analysis Timing (Substudy C)	Updated timing of analysis	Due to change in overall substudy design.	Substantial
Section 10.9.9.5 Sample Size Determination (Substudy C)	Confirmed the sample size is not based on any formal hypothesis test	Due to change in overall substudy design.	Substantial
Section 10.9.9.5 Sample Size Determination (Substudy C)	Updated Table 9 based on revised enrollment	Due to change in overall substudy design.	Substantial
Section 10.10.1.2.1 Schema Cohort 1 (Substudy D)	12-month follow-up visit removed	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.10.1.2.2 Schema Cohort 2 (Substudy D)	12-month follow-up visit removed	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.10.1.3.1 Schedule of Activities Cohort 1 (Substudy D)	12-month follow-up visit removed	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.10.1.3.2 Schedule of Activities Cohort 2 (Substudy D)	12-month follow-up visit removed	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.10.2.1 Study Rationale (Substudy D)	Confirmed active participants in Cohort 1 and Cohort 2 at the time of this amendment will only be followed for 6 months after their last study vaccination. Their final visit will be V405. For participants who have already completed V405 at the time of protocol amendment 11, they will be informed by the investigator site staff of study completion and that no further visits are required	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.10.3 Objectives, Estimands, and Endpoints (Substudy D)	Confirmed participants will not be age-matched to participants in C4591001, but will include similar percentage of participants with baseline-positive SARS-CoV-2 infection status as Group 5 of Substudy D, whenever feasible	In response to feedback received from CBER.	Nonsubstantial
Section 10.10.4.1 Study Design (Substudy D)	Confirmed active participants in Cohort 1 and Cohort 2 at the time of this amendment will only be followed for 6 months after their last study vaccination. Their final visit will be V405	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.10.8 Study Assessments and Procedures (Substudy D)	Clarified total blood sampling volume	Volume reduced due to removal of 12-month follow-up visit.	Substantial
Section 10.10.8.6.1.5 Visit 405 (Substudy D)	Clarified for participants who have already completed V405 at the time of protocol amendment 11 that they will be informed by the investigator site staff of study completion	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required and V406 was removed.	Substantial
Section 10.10.8.6.1.5 Visit 405 (Substudy D)	Confirmed the e-diary will be collected or the participant assisted to remove the study application from his or her own personal device, and reference to ensuring the participant has a self-swab kit was removed	V405 is now the final study visit for Cohort 1 and Cohort 2 as they will now only be followed for the safety reporting period of 6 months after the last dose.	Substantial
Section 10.10.8.6.1.6 Visit 406 (Substudy D)	12-month follow-up visit removed	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.10.8.6.2.7 Visit 405 (Substudy D)	Clarified for participants who have already completed V405 at the time of protocol amendment 11 that they will be informed by the investigator site staff of study completion	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required and V406 was removed.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.10.8.6.2.7 Visit 405 (Substudy D)	Confirmed the e-diary will be collected or the participant assisted to remove the study application from his or her own personal device, and reference to ensuring the participant has a self-swab kit was removed	V405 is now the final study visit for Cohort 1 and Cohort 2 as they will now only be followed for the safety reporting period of 6 months after the last dose.	Substantial
Section 10.10.8.6.2.8 Visit 406 (Substudy D)	12-month follow-up visit removed	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.10.9.4.1 Analysis Timing (Substudy D)	Deleted the safety and immunogenicity analysis 12 months after the last study vaccination	The safety follow-up period is 6 months after the last dose, therefore a longer study duration is not required.	Substantial
Section 10.11.8.6.1 Screening (Substudy E)	Deleted reference to AEs that occur prior to dosing being recorded on the medical history CRF	For consistency with Section 8.3 .	Nonsubstantial
Section 10.12.3 Objectives, Endpoints, and Estimands (Substudy F)	Updated the seroresponse definition to achieving ≥ 4 -fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times \text{LLOQ}$ is considered seroresponse	To align with the definition used in other substudies within C4591031.	Nonsubstantial
Section 10.12.3 Objectives, Endpoints, and Estimands (Substudy F)	Clarified that PBMC analysis will include B-cell characterization, and that RBD binding IgG and RBD binding IgA will also be tested	To further clarify the testing to be performed.	Nonsubstantial
Section 10.12.3 Objectives, Endpoints, and Estimands (Substudy F)	Added the following endpoint: GMRs at each time point after the study vaccination between different vaccine groups	To further clarify the analyses to be performed.	Substantial
Section 10.12.8.2 Immunogenicity (Substudy F)	Removed details on PBMC analysis as the analyses to be performed are detailed in Section 10.12.9	To further clarify the testing to be performed.	Nonsubstantial
Section 10.12.9.3.1 General Considerations (Substudy F)	Added a section, "Adjusted Comparisons of Antibody Levels"	To further clarify the analyses to be performed.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.12.9.3.2 Primary Endpoint(s)/Estimand(s) Analysis (Substudy F)	Added the following analysis: model-based GMRs at each time point after the study vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group (using the BNT162b2 30-µg group as the reference)	To further clarify the analyses to be performed.	Nonsubstantial
Section 10.12.9.3.3 Exploratory Endpoint(s)/Estimand(s) Analysis (Substudy F)	Added the following analysis: model-based GMRs of neutralizing titers for VOCs not already analyzed as a primary outcome at a specific time point after the study vaccination, along with the associated 2-sided 95% CIs, may be provided for each vaccine group (using the BNT162b2 30-µg group as the reference)	To further clarify the analyses to be performed.	Nonsubstantial
Section 10.12.9.4.1 Analysis Timing (Substudy F)	Added safety and immunogenicity data analysis through 3 months after study vaccination for each group	To further clarify the analyses to be performed.	Nonsubstantial

Amendment 10 (22 July 2022)

Overall Rationale for the Amendment:

Initial immunogenicity data reviewed from Cohort 3 Substudy D at 1 month after Dose 2 demonstrated a more pronounced antibody response against the Omicron variant versus the Wild Type and Delta variants. Therefore, the third dose for participants in Cohort 3 of Substudy D has been changed from BNT162b2 OMI 30 µg to BNT162b2 30 µg to provide participants with wider protection against the different SARS-CoV-2 variants, in addition to the protection they will already have against the Omicron variant from their first 2 vaccinations.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 – Synopsis and Section 10.10.4.1 – Overall Design (Substudy D)	Confirmed that if participants do not consent to receive BNT162b2 as a third dose, they will not receive a third dose	Protocol clarification	Substantial
Section 10.10.6.1.1 – Administration (Substudy D)	Clarified that participants in Cohort 3 will receive BNT162b2 rather than BNT162b2 OMI as their third dose	Protocol clarification	Substantial
Section 10.10.8 – Study Assessments and Procedures (Substudy D)	Clarified that participants in Cohort 3 will receive BNT162b2 rather than BNT162b2 OMI as their third dose	Protocol clarification	Substantial
Section 10.10.1.3.3 – Cohort 3 schedule of activities (Substudy D)	Confirmed that the vaccine received at Visit 506 is BNT162b2	Protocol clarification	Substantial
Section 10.10.2.1 – Study Rationale (Substudy D)	Clarified that participants in Cohort 3 will receive BNT162b2 rather than BNT162b2 OMI as their third dose	Protocol clarification	Substantial
Section 10.8.8.3.5 – Visit 205 – 1 Month Follow-Up Visit (After Vaccination 2) (28-35 Days After Visit 203) (Substudy B)	Confirmed that a participant may be unblinded at Visit 205, 1 month after receiving their second study vaccination, to confirm the date of BNT162b2 receipt	Protocol clarification	Substantial
Section 10.10.1.2.3 – Participants in Cohort 3 schema (Substudy D)	Confirmed that the vaccine received at the 6-month visit is BNT162b2	Protocol clarification	Substantial
Section 1.1 – Synopsis, Section 10.10.1.2 – Schema, Section 10.10.1.3 – Schedule of Activities for Substudy D, Section 10.10.2.1 – Study Rationale, Section 10.10.4 – Study Design, Section 10.10.6.1.1 – Administration, and Section 10.10.8 – Study Assessments and Procedures (Substudy D)	Clarified that participants in Cohort 3 will receive BNT162b2 rather than BNT162b2 OMI as their third dose	Protocol clarification	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 – Synopsis, Section 10.8.1.2 – Schema, Section 10.8.1.3 – Schedule of Activities for Substudy B, Section 10.8.2.1 – Study Rationale, Section 10.8.4 – Study Design, Section 10.8.5.1 – Inclusion Criteria, and Section 10.8.8.3 – Substudy B Procedures (Substudy B)	Added the number of days since the last dose, in parentheses after the number of months	Protocol clarification	Nonsubstantial
Section 1.1 – Synopsis, Section 10.9.1.2 – Schema, Section 10.9.1.3 – Schedule of Activities for Substudy C, Section 10.9.2.1 – Study Rationale, Section 10.9.4 – Study Design, and Section 10.9.8.4 – Substudy C Procedures (Substudy C)	Added the number of days since the last dose, in parentheses after the number of months	Protocol clarification	Nonsubstantial
Section 1.1 – Synopsis, Section 10.11.4 – Study Design, and Section 10.11.5.1 – Inclusion Criteria (Substudy E)	Added the number of days since the last dose, in parentheses after the number of months	Protocol clarification	Nonsubstantial
Section 10.7.3 – Objectives, Estimands, and Endpoints (Substudy A)	Deleted the objective for efficacy against asymptomatic SARS-CoV-2 infection	Protocol clarification	Nonsubstantial
Section 10.7.8.1.2 – Efficacy Against Asymptomatic SARS-CoV-2 Infection (Substudy A)	Deleted the section on efficacy against asymptomatic SARS-CoV-2 infection	Protocol clarification	Nonsubstantial
Section 10.7.9.3.3 – Secondary Endpoints(s)/Estimand(s) Analysis (Substudy A)	Deleted the objective for efficacy against asymptomatic SARS-CoV-2 infection	Protocol clarification	Nonsubstantial
Section 10.8.5.2 – Exclusion Criteria, Other Exclusions (Substudy B)	Clarified that prior receipt of more than 3 doses of BNT162b2 30 µg is an exclusion	Protocol clarification	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.8.8.3.3 – Visit 203 –Vaccination 2 (28 to 35 Days After Visit 201) (Substudy B)	Confirmed that a positive SARS-CoV-2 NAAT result without symptoms, or a COVID-19 diagnosis, should not result in discontinuation of study intervention	Protocol clarification	Nonsubstantial
Section 10.10.1.3.3 – Cohort 3 schedule of activities (Substudy D)	Extended the visit window by 7 days to 199 days after Visit 502	Protocol clarification	Nonsubstantial
Section 10.10.3 – Objectives, Estimands, and Endpoints (Substudy D)	Added Group 5 to the objectives and clarified the estimands to include those with or without serological or virological evidence of past SARS-CoV-2 infection	Clarified objectives and estimands	Nonsubstantial
Section 10.10.8.6.1.2 – Visit 402 – 1-Month Follow-Up Visit (After Substudy D Vaccination 1) (28 to 35 Days After Visit 401) (Substudy D)	Confirmed that a positive SARS-CoV-2 NAAT result without symptoms, or a COVID-19 diagnosis, should not result in discontinuation of study intervention	Protocol clarification	Nonsubstantial
Section 10.10.8.6.2.3 – Visit 404 – 3-Month Follow-Up Visit (85 to 95 Days After Visit 401, or 85 to 123 Days After Visit 401 for Those Participants Who Consent to Receive Substudy D Vaccination 2) (Substudy D)	Confirmed that a positive SARS-CoV-2 NAAT result without symptoms, or a COVID-19 diagnosis, should not result in discontinuation of study intervention	Protocol clarification	Nonsubstantial
Section 10.10.8.6.3.2 – Visit 502 – Vaccination 2 (19 to 23 Days After Visit 501) (Substudy D)	Confirmed that a positive SARS-CoV-2 NAAT result without symptoms, or a COVID-19 diagnosis, should not result in discontinuation of study intervention	Protocol clarification	Nonsubstantial
Section 10.10.8.6.3.6 – Visit 506 – 6-Month Follow-Up Visit (After Vaccination 2) (150 to 199 Days After Visit 502) and Administration of Vaccination 3 (Substudy D)	Confirmed that a positive SARS-CoV-2 NAAT result without symptoms, or a COVID-19 diagnosis, should not result in discontinuation of study intervention	Protocol clarification	Nonsubstantial
Section 10.10.9.3.2 – Primary Endpoint(s)/Estimand(s) Analysis (Substudy D)	Updated an immunogenicity endpoint to specify the Cohort 1 and 2 participants to be used in analysis	Clarified primary endpoints	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.11.3 – Objectives, Estimands, and Endpoints (Substudy E)	Clarified an exploratory objective’s footnote to specify that the subset taken will be from the youngest 150 participants in Substudy E who received bivalent BNT162b2	Clarified the subset of participants to be selected for the exploratory objective	Nonsubstantial
Section 10.11.9.1.2 – Statistical Hypotheses (Substudy E)	Clarified that the primary and secondary immunogenicity objectives for participants >55 years of age will be evaluated by the statistical hypotheses described in the section, and the immunogenicity objectives for participants 18 through 55 years of age are descriptive only	Clarified the statistical hypotheses	Nonsubstantial
Section 10.11.9.1.3 – Multiplicity Adjustment (Substudy E)	Clarified the age ranges for the objectives	To clarify the age ranges to use multiplicity adjustments	Nonsubstantial
Section 10.11.9.3 – Statistical Analyses (Substudy E)	Confirmed that a sensitivity analysis of GMR and difference in seroresponse rate for between-group comparison may be performed	Clarified additional analyses being performed	Nonsubstantial

Amendment 9 (03 May 2022)

Overall Rationale for the Amendment:

The inclusion criteria for Substudy B have been updated to allow participants who have received a third dose of BNT162b2 at least 4 months prior to randomization, to support enrollment and to align with current recommendations.

Substudy E has been amended to obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in participants 18 to 55 years of age.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 1.1 – Synopsis, Substudy E	Added sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E and updated the number of participants to 2910 for Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.8.1.2 – Schema for Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 10.8.1.3 – SoA for Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 10.8.2.1 – Study Rationale for Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 10.8.4.1 – Overall Design for Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.

Section # and Name	Description of Change	Brief Rationale
Section 10.8.5.1 – Inclusion Criteria for Substudy B	Updated criteria to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 10.8.8.3.1 – Visit 201 for Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 10.10.8.6.2.3 – Visit 404 for Substudy D	Moved the following text and changed it from a procedure to a note: Participants in Cohort 2 will be unblinded to confirm the vaccine received once they have COMPLETED Visit 404 (3 months after Substudy D Vaccination 1). Since these are the only participants still blinded at this time, the study team will also become unblinded to all participants' original study intervention allocation at this time.	To prevent sites from unblinding participants prematurely.
Section 10.11.1.2 – Schema for Substudy E	Added sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.1.3 – SoA for Substudy E	Added sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.3 – Objectives, Estimands, and Endpoints for Substudy E	Updated the primary and secondary objectives with respect to noninferiority of the seroresponse rate and updated the definition of seroresponse and added text and objectives for the 18- to 55-year-olds.	To align with regulatory requirements and to describe the analysis of data from 18- to 55-year-olds.

Section # and Name	Description of Change	Brief Rationale
Section 10.11.4 – Overall Design for Substudy E	Added text to include sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.5.1 – Inclusion Criteria for Substudy E	Updated inclusion criterion 1 for sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E. Added a new exclusion criterion for sentinel participants in Groups 7 to 9 requiring that screening troponin levels must be within normal range prior to randomization.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.6 – Study Intervention(s) and Concomitant Therapy for Substudy E	Added text to include sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.8 – Study Assessments and Procedures for Substudy E	Added text to specify that sentinel cohort participants in Groups 7, 8, and 9 will also have 20 mL of blood drawn for troponin levels.	Troponin levels will be obtained at screening and on Day 3.
Section 10.11.8.2 – Immunogenicity for Substudy E	Added text to specify that up to approximately 90 participants across the 18- to 55-year-old groups (Groups 7 to 9) will contribute to PBMC sample collection.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.8.6 – Substudy E Procedures	Added text to include sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.9 – Statistical Considerations for Substudy E	Updated hypotheses, multiplicity, analysis, and sample size calculation related to changes in objectives and added text and objectives for the 18- to 55-year-olds.	To align with regulatory requirements and to describe the analysis of data from 18- to 55-year-olds.

Amendment 8 (31 Mar 2022)

Overall Rationale for the Amendment:

Added language to permit early discontinuation of participants in Substudy A for reasons including (but not limited to) access and availability of BNT162b2 in the real world, reducing the need for participant involvement and observation in this clinical trial.

Substudy B was updated to clarify that participants may be unblinded to confirm the dose of BNT162b2 received at Visit 205, 1 month after receiving their second study vaccination. This amendment will allow for collection of data after a dose of BNT162b2 OMI at Visit 404 in Substudy D Group 3 and Group 4 participants who received 3 prior doses of BNT162b2 and a fourth dose of either BNT162b2 or BNT162b2 OMI. Substudy D updates also include changes to the statistical considerations to align with CBER feedback.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis, Rationale	Updated text to state that to date, more than 455 million people have been infected with SARS-CoV-2 and >6 million have died.	To provide the most current information.
Section 1.1 – Synopsis, Substudy A Design	Added language to permit early discontinuation of participants in Substudy A.	Due to access and availability of BNT162b2 in the real world, and for participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program.
Section 1.1 – Synopsis, Substudy D Design	Added text for Cohort 2 to clarify that participants will be offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up). Removed text stating that Group 4 may not be enrolled.	To allow for collection of data after a dose of BNT162b2 OMI at Visit 404 in participants who received 3 prior doses of BNT162b2 and a fourth dose of either BNT162b2 or BNT162b2 OMI. Group 4 was enrolled.
Section 2.2 – Background	Updated text to state that to date, more than 455 million people have been infected with SARS-CoV-2 and >6 million have died.	To provide the most current information.
Section 8.3.1 – Time Period and Frequency for Collecting AE and SAE Information, Substudy D	Added text to clarify the AE collection time period for Group 3 and Group 4 participants who will receive a dose of BNT162b2 OMI at Visit 404.	To account for a dose of BNT162b2 OMI administered to Group 3 and Group 4 participants at Visit 404.

Section # and Name	Description of Change	Brief Rationale
Section 10.7.4 – Study Design for Substudy A	Added language to permit early discontinuation of participants in Substudy A.	Due to access and availability of BNT162b2 in the real world, and for participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program.
Section 10.8.6.2.2 – Blinding of the Sponsor for Substudy B	Added text to clarify that the participant may be unblinded to confirm the dose of BNT162b2 received at Visit 205, 1 month after receiving their second study vaccination. The study team will also become unblinded to the participant's original study intervention allocation at this time.	To allow participants to add the vaccination details to their national vaccination record cards.
Section 10.8.8.3.3 - Visit 203 – Vaccination 2 (28 to 35 Days After Visit 201) for Substudy B	Addition of the step to measure the participant's body temperature.	Protocol clarification.
Section 10.9.8.4.3 Visit 303 – 1 Month After Booster Vaccination (28 to 35 Days After Visit 301) for Substudy C	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.9.3 – Objectives, Estimands, and Endpoints for Substudy C	Corrected the age group ranges in the second primary immunogenicity objective: 18 through 30 years of age and 31 through 55 years of age.	To correct a typographical error in the previous version.
Section 10.9.9.3.4 – Exploratory Endpoint(s) Analysis for Substudy C	Removed “anti” from anti-VOC neutralizing titers, as the term “anti” in this context is extraneous.	To correct a typographical error in the previous version.
Section 10.10.1.2.1 – Schema for Substudy D	Added a row to confirm the participant's prior study and participant number (if applicable) should be recorded in the CRF.	Protocol clarification.
Section 10.10.1.2.2 – Schema for Substudy D	Added a separate schema for Cohort 2 participants.	To account for the second dose of BNT162b2 OMI administered to Group 3 and 4 participants.
Section 10.10.1.3 – Schedule of Activities for Substudy D	Added a separate schedule of activities for Cohort 2 participants.	To account for the second dose of BNT162b2 OMI administered to Group 3 and 4 participants.
Section 10.10.3 – Objectives, Estimands, and Endpoints for Substudy D	Updated the primary and secondary objectives with respect to noninferiority of the seroresponse rate and updated the definition of seroresponse.	To align with regulatory requirements.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.4.1 – Study Design for Substudy D	Added text for Cohort 2 participants to clarify that they will be offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up). Removed text stating that Group 4 may not be enrolled.	To allow for collection of data after a dose of BNT162b2 OMI at Visit 404 in participants who received 3 prior doses of BNT162b2 and either a fourth dose of BNT162b2 or BNT162b2 OMI. Group 4 was enrolled.
Section 10.10.6.1.1 – Administration for Substudy D	Added text to indicate that Group 3 and Group 4 participants may receive a dose of BNT162b2 OMI at Visit 404.	To account for a dose of BNT162b2 OMI administered to Group 3 and Group 4 participants at Visit 404.
Section 10.10.6.2.1 – Blinding of the Site Personnel for Substudy D	Added text to allow Cohort 2 to be unblinded at Visit 404.	To allow participants to add the vaccination details to their national vaccination record cards.
Section 10.10.6.2.2 – Blinding of the Sponsor for Substudy D	Added text to allow Cohort 2 to be unblinded at Visit 404.	To allow participants to add the vaccination details to their national vaccination record cards.
Section 10.10.8.6 – Substudy D Procedures	Added a subsection of procedures for Cohort 2.	To account for a dose of BNT162b2 OMI administered to Group 3 and Group 4 participants.
Section 10.10.8.6.1.2 Visit 402 – 1-Month Follow-Up Visit (After Substudy D Vaccination 1) (28 to 35 Days After Visit 401) for Substudy D	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.10.8.6.1.3 Visit 403 – 1-Month Follow-Up Visit (After Substudy D Vaccination 2) (28 to 35 Days After Visit 402) for Substudy D	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.10.8.6.3.4 Visit 504 – 1-Month Follow-Up Visit (After Vaccination 2) (28 to 35 Days After Visit 502) for Substudy D	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.10.8.6.3.7 Visit 507 – 1-Month Follow-Up Visit (After Vaccination 3) (28 to 35 Days After Visit 506) for Substudy D	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.8.6.6 – SARS-CoV-2 NAAT Results for Substudy D	Added Visit 404 (Group 3 and Group 4 participants who receive a dose of BNT162b2 OMI at Visit 404) to the list of nasal swab visit time points that will be used to determine whether a participant will be included in the immunogenicity analysis. Clarified the analysis (immunogenicity) and time points of those with no serological or virological evidence (up to 1 month after receipt of the third, fourth, or fifth dose for BNT162b2-experienced participants, or as a 2-dose series to COVID-19 vaccine-naïve participants) of past SARS-CoV-2 infection.	To account for the dose of BNT162b2 OMI administered to Group 3 and Group 4 participants at Visit 404. To correct the analysis population and time points of past SARS-CoV-2 infection.
Section 10.10.9 – Statistical Considerations for Substudy D	Updated hypotheses, multiplicity, analysis, and sample size calculation related to changes in objectives.	To align with regulatory requirements.
Section 10.10.9.3.4 – Exploratory Endpoint(s) Analysis for Substudy D	Removed “anti” from anti-VOC neutralizing titers, as the term “anti” in this context is extraneous.	To correct a typographical error in the previous version.
Section 10.11.4.1 – Overall Design for Substudy E	Added group number to the Sentinel and Expanded Enrollment table.	To provide more clarity when referring to groups in the Statistical Considerations section.
Section 10.11.8.6.5 Visit 603 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 601) for Substudy E	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.11.9.3.4 – Exploratory Endpoint(s) Analysis for Substudy E	Removed “anti” from anti-VOC neutralizing titers, as the term “anti” in this context is extraneous.	To correct a typographical error in the previous version.
Section 10.12.8.5.3 Visit 703 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 701) for Substudy F	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.12.9.3.3 – Exploratory Endpoint(s) Analysis for Substudy F	Removed “anti” from anti-VOC neutralizing titers as the term “anti” in this context is extraneous.	To correct a typographical error in the previous version.
Section 10.12.9.4.1 – Analysis Timing for Substudy F	Removed the analysis for immunogenicity data through 7 days after study vaccination for each group and safety data through 7 days after study vaccination for each group.	Data from Substudy E will be used to inform decisions at this immunogenicity time point. Safety data at 7 days after study vaccination are covered by the IRC review.

Amendment 7 (17 Feb 2022)

Overall Rationale for the Amendment:

A BNT162b2 bivalent (BNT162b2 Wild Type and BNT162b2 OMI) formulation will be available as a preformulated product in Substudy E. The sentinel-cohort participants randomized to the combination BNT162b2 and BNT162b2 OMI groups will be administered a suspension containing a mixture of BNT162b2 Wild Type and BNT162b2 OMI prepared from 2 separate vials at the investigator site. Participants in the expanded cohort who are randomized to the combination BNT162b2 and BNT162b2 OMI groups will receive the preformulated product containing BNT162b2 Wild Type and BNT162b2 OMI.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Section 10.10.9.3.2 – Primary Endpoint(s)/Estimand(s) Analysis for Substudy D	Updated text to clarify that superiority based on GMR will be established if the lower bound of the 2-sided 97.5% CI for the GMR is >1.	To correct a typographical error in the previous version.
Section 10.10.6.2 – Measures to Minimize Bias: Randomization and Blinding for Substudy D	Removed “(Cohort 2 Only)” from the header as the text included in the subsections referenced Cohort 1 as well.	To clarify that the section contains text for Cohort 1.
Section 10.9.6.2.2 – Blinding of the Sponsor for Substudy D	Added text to clarify sponsor blinding to Cohort 1, Groups 1 and 2b, as specified elsewhere within this subsection.	To clarify and reiterate sponsor blinding to Cohort 1, Groups 1 and 2b.
Section 10.11.4 – Study Design for Substudy E	Updated footnotes to clarify that the sentinel-cohort participants randomized to the combination BNT162b2 and BNT162b2 OMI groups will receive doses that are prepared at the investigator site from 1 vial each of diluted BNT162b2 vaccine and BNT162b2 OMI vaccine. Participants in the expanded cohort who are randomized to the combination BNT162b2 and BNT162b2 OMI groups will receive the doses from a single 100-µg/mL vial of BNT162b2 bivalent [Wild Type and Omicron (B.1.1.529)] preformulated vaccine suspension for injection. No dilution is required	To study a preformulated BNT162b2 bivalent mixture of BNT162b2 Wild Type and BNT162b2 OMI.

Section # and Name	Description of Change	Brief Rationale
Section 10.11.6 – Study Intervention(s) and Concomitant Therapy for Substudy E	Updated text to clarify that the sentinel-cohort participants randomized to the combination BNT162b2 and BNT162b2 OMI groups will be administered a suspension containing a mixture of BNT162b2 Wild Type and BNT162b2 OMI prepared from 2 separate diluted vials at the investigator site. Participants in the expanded cohort who are randomized to the combination BNT162b2 and BNT162b2 OMI groups will receive the preformulated bivalent mixture from a single vial (no dilution required).	To study a preformulated BNT162b2 bivalent mixture of BNT162b2 Wild Type and BNT162b2 OMI.
Section 10.11.6.1 – Study Intervention(s) Administered for Substudy E	Added a column to the table to account for the preformulated BNT162b2 bivalent [Wild Type and Omicron (B.1.1.529)] vaccine that will be administered to the expanded-enrollment participants from a preformulated single vial (no dilution required). Clarified text in the footnotes to align with the study design section.	To study a preformulated BNT162b2 bivalent mixture of BNT162b2 Wild Type and BNT162b2 OMI. Administrative change to clarify and align with the study design section.
Section 10.12.6.1 – Study Intervention(s) Administered for Substudy F	Clarified text in the footnotes to align with the study design section.	Administrative change to clarify and align with the study design section.

Amendment 6 (08 Feb 2022)

Overall Rationale for the Amendment:

The primary and secondary objectives and statistical parameters for Substudy D will be modified to include superiority analyses to align with regulatory requirements.

This amendment also includes updates to the inclusion criteria to both Substudy B and Substudy C to reduce the time period of the second dose of prior BNT162b2 to 5 months prior to randomization for all participants. Updates to inclusion criteria for Substudy D and Substudy E were made to increase the eligible population.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis, Substudy B Design	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 1.1 – Synopsis, Substudy C Design	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization instead of 6 months prior for all participants.	To align with regulatory feedback and current recommendations.
Section 1.1 – Synopsis, Substudy D Design	<p>Updated text to clarify that participants in Cohort 3 may receive their third dose of BNT162b2 OMI as early as 5 months after their second dose.</p> <p>Removed the statement that stratification by age will be managed by the IRT system to ensure a similar distribution of age strata across the 3 cohorts.</p> <p>Updated text to clarify that participants in Cohort 1 will have completed a 2-dose primary series of BNT162b2 (30-µg doses), with their last dose 90 to 240 days prior to enrollment.</p>	<p>To align with regulatory feedback and current recommendations.</p> <p>Text regarding stratification by age was removed as it is already included in the descriptions of the cohorts.</p> <p>To increase the eligible population.</p>
Section 1.1 – Synopsis, Substudy E Design	Updated text to state that participants who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 5 to 12 months prior to randomization, will be enrolled. The previous prior BNT162b2 window was 6 to 12 months.	To increase the eligible population.
Section 10.8.1.2 – Schema for Substudy B	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.8.1.3 – Schedule of Activities for Substudy B	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.

Section # and Name	Description of Change	Brief Rationale
Section 10.8.2 – Rationale for Substudy B	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.8.4 – Study Design for Substudy B	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.8.5.1 – Inclusion Criteria for Substudy B	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 150 days prior to Visit 201 for all participants. Inclusion criterion 1 was combined into a single bullet as this new window applies to all age groups in Substudy B.	To align with regulatory feedback and current recommendations.
Section 10.8.8.3.1 – Substudy B Procedures, Visit 201	Updated text asking to confirm that the participant has only received 2 doses of BNT162b2 at least 5 months prior to randomization.	To align with regulatory feedback and current recommendations.
Section 10.9.1.2 – Schema for Substudy C	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.9.1.3 – Schedule of Activities for Substudy C	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.9.2 – Rationale for Substudy C	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.9.3 – Objectives, Estimands, and Endpoints for Substudy C	Updated the control group for noninferiority to age-matched participants randomly selected from C4591001.	To align with the removal of the requirement that participants 12 to 17 years of age must have received 2 prior doses of BNT162b2 in C4591001.

Section # and Name	Description of Change	Brief Rationale
Section 10.9.4 – Study Design for Substudy C	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization instead of 6 months prior for all participants.	To align with regulatory feedback and current recommendations.
Section 10.9.5.1 – Inclusion Criteria for Substudy C	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 150 days prior to Visit 301 for all participants. Removed the requirement that participants 12 to 17 years of age must have received 2 prior doses of BNT162b2 in C4591001.	To align with regulatory feedback and current recommendations. To permit enrollment of participants who did not participate in C4591001.
Section 10.9.8.4.1 – Substudy C Procedures, Visit 301	Updated text asking to confirm the participant has only received 2 doses of BNT162b2 at least 5 months prior to randomization.	To align with regulatory feedback and current recommendations.
Section 10.9.9 – Statistical Considerations for Substudy C	Modified the statistical considerations including the hypothesis, general considerations, objectives, estimands, endpoints, and comparisons.	To align with the removal of the requirement that participants 12 to 17 years of age must have received 2 prior doses of BNT162b2 in C4591001.
Section 10.10.1.2.1 – Schema for Substudy D, Participants in Cohorts 1 and 2	Updated text to clarify that Cohort 1 participants must have received 2 doses of BNT162b2 before enrollment (3-8 months after last dose).	To increase the eligible population.
Section 10.10.1.2.2 – Schema for Substudy D, Participants in Cohort 3	Added a footnote to clarify that participants in Cohort 3 may receive their third dose of BNT162b2 OMI as early as 5 months after their second dose.	To align with regulatory feedback and current recommendations.
Section 10.10.1.3.1 – Schedule of Activities for Substudy D, Cohorts 1 and 2	Added a row for the following procedure: Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs. Updated text to clarify that Cohort 1 participants must have received 2 doses of BNT162b2 before enrollment (3-8 months after last dose).	To provide clarification on expectations for site personnel regarding self-swabs. To increase the eligible population.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.1.3.2 – Schedule of Activities for Substudy D, Cohort 3	<p>Added footnote to clarify that participants in Cohort 3 may receive their third dose of BNT162b2 OMI as early as 5 months after their second dose. Updated the early part of the Visit 506 window to 150 days after Vaccination 2.</p> <p>Added a row for the following procedure: Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs.</p>	<p>To align with regulatory feedback and current recommendations.</p> <p>To provide clarification on expectations for site personnel regarding self-swabs.</p>
Section 10.10.2.1 – Study Rationale for Substudy D	Corrected “2 doses” to “3 doses” of BNT162b2 OMI.	This was an administrative change to correct a typo.
Section 10.10.3 – Objectives, Estimands, and Endpoints for Substudy D	Updated the primary and secondary objectives. Superiority added as a primary immunogenicity objective. Noninferiority and “super” superiority added as secondary immunogenicity objectives. Exploratory objectives and footnotes were modified.	To align with regulatory requirements.
Section 10.10.4 – Study Design for Substudy D	<p>Updated text to clarify that participants in Cohort 3 may receive their third dose of BNT162b2 OMI as early as 5 months after their second dose.</p> <p>Updated text to clarify that Cohort 1 participants must have received 2 prior doses of 30 µg BNT162b2, with the second dose being 90 to 240 days before Visit 401 (Day 1).</p> <p>Removed the statement that stratification by age will be managed by the IRT system to ensure a similar distribution of age strata across the 3 cohorts.</p>	<p>To align with regulatory feedback and current recommendations.</p> <p>To increase the eligible population.</p> <p>Text regarding stratification by age was removed as it is already included in the descriptions of the cohorts.</p>
Section 10.10.5.1 – Inclusion Criteria for Substudy D	Updated inclusion criteria for Cohort 1 participants to state that participants must have received 2 prior doses of 30 µg BNT162b2, with the second dose being 90 to 240 days before Visit 401 (Day 1).	To increase the eligible population.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.8.6 –Substudy D Procedures	Added details regarding the self-swabs to clarify that sites must provide/ensure the participant has a nasal self-swab kit and provide instructions on self-collection of nasal swabs.	To provide clarification on expectations for site personnel regarding self-swabs.
Section 10.10.6.1.1 – Administration for Substudy D	Added the following text: Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.	To align with regulatory feedback and current recommendations.
Section 10.10.8.6.2 – Administration of BNT162b2 OMI to COVID-19 Vaccine-Naïve Participants (Cohort 3) for Substudy D	Updated text to clarify that participants will receive 2 doses (primary series) of BNT162b2 OMI, separated by 21 days, with a third dose approximately 5 months later.	Administrative change and to align with regulatory feedback and current recommendations.
Section 10.10.8.6.2.6 – Administration of BNT162b2 OMI to COVID-19 Vaccine-Naïve Participants (Cohort 3), Visit 506 for Substudy D	Updated text to clarify that Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.	To align with regulatory feedback and current recommendations.
Section 10.10.9 – Statistical Considerations for Substudy D	Updated the primary and secondary objectives to include superiority and “super” superiority. Additional changes were made to the statistical hypothesis, multiplicity adjustment, general considerations and comparisons.	To align with regulatory requirements.
Section 10.11.1.3 – Schedule of Activities for Substudy E	Added a row for the following procedure: Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs.	To provide clarification on expectations for site personnel regarding self-swabs.
Section 10.11.4 – Study Design for Substudy E	Updated text to state that participants who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 5 to 12 months prior to randomization, will be enrolled. The previous prior BNT162b2 window was 6 to 12 months.	To increase the eligible population.
Section 10.11.5.1 – Inclusion Criteria for Substudy E	Updated inclusion criteria to state that participants who have received 3 prior doses of 30 µg BNT162b2, with the third dose being 5 to 12 months before Visit 601 (Day 1). The previous prior BNT162b2 window was 6 to 12 months.	To increase the eligible population.

Section # and Name	Description of Change	Brief Rationale
Section 10.11.8.6 –Substudy E Procedures	Added details regarding the self-swabs to clarify that sites must provide/ensure the participant has a nasal self-swab kit and provide instructions on self-collection of nasal swabs.	To provide clarification on expectations for site personnel regarding self-swabs.
Section 10.12.1.3 – Schedule of Activities for Substudy F	Added a row for the following procedure: Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs.	To provide clarification on expectations for site personnel regarding self-swabs.
Section 10.12.8.5 –Substudy F Procedures	Added details regarding the self-swabs to clarify that sites must provide/ensure the participant has a nasal self-swab kit and provide instructions on self-collection of nasal swabs.	To provide clarification on expectations for site personnel regarding self-swabs.

Amendment 5 (20 Jan 2022)

Overall Rationale for the Amendment:

The SARS-CoV-2 variant B.1.1.529, also known as Omicron, is currently the dominant variant in many countries and within the US is responsible for 95.4% of sequenced COVID-19 cases. Current data note that the vaccine effectiveness against hospitalization is 88% (78%-93%) for Omicron after 3 doses of vaccine. However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant. The addition of a higher-dose booster may improve protection, particularly in older individuals, with increased longevity of an immune response, provided it has a tolerable safety profile. Therefore, Substudies E and F have been designed to evaluate high-dose BNT162b2 OMI (60 µg), high-dose BNT162b2 (60 µg), and a high-dose combination of BNT162b2 OMI and BNT162b2 (30 µg of each) compared to BNT162b2 OMI 30 µg, BNT162b2 30 µg, and a combination of BNT162b2 OMI and BNT162b2 (15 µg of each), given as a fourth dose.

This amendment also incorporates the addition of a BNT162b2 30-µg dose group (given as a third dose) to Cohort 1 in Substudy D. In this group, 205 participants will be enrolled to provide a contemporaneous third-dose control group for analyses and comparisons.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Sections 1 through 9	Cross-reference to sections within Substudies E and F added where required and throughout.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 1.1 – Synopsis, Substudy D Design	Addition of description of Group 2b (1 dose of BNT162b2), updated total number of participants to 1420, updated Cohort 1 participant total to 615, and updated the table to include Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 1.1 – Synopsis, Substudy D Number of Participants	Updated the number of participants to 615 for Cohort 1.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 1.1 – Synopsis, Overall Design	Addition of design of Substudies E and F, number of participants, and specified that an IRC will be used for Substudies E and F.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 1.1 – Synopsis, Substudies E and F Number of Participants	Addition of Substudies E and F, number of participants.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 1.1 – Synopsis, Data Monitoring Committee or Other Independent Data Monitoring Committee	Addition of DMC and IRC details for Substudies E and F.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 2.2 – Background	Addition of Substudies E and F.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.

Section # and Name	Description of Change	Brief Rationale
Section 2.3 – Risk Assessment	Added additional mitigations for Substudies E and F and updated existing mitigations to align with the study designs for Substudies D, E, and F.	Substudies E and F have a higher dose level of study vaccine, and additional mitigations have been put in place. Existing mitigations were updated to account for the dosing schedules for Substudies D, E, and F.
Section 4.3 – Justification for Dose	Addition of justification for dose levels in Substudies E and F.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 8.3.1 – Time Period and Frequency for Collecting AE and SAE Information – Substudy D	Addition of Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 8.3.1 – Time Period and Frequency for Collecting AE and SAE Information – Substudies E and F	Confirmation of the safety reporting time periods for Substudies E and F.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Sections 10.7.9.4 – Interim Analysis and 10.7.9.4.1 – Analysis Timing for Substudy A	Removed efficacy and safety analysis when all participants completed blinded follow-up and added that additional analyses may be conducted if required for regulatory purposes. Removed the requirement to conduct interim analyses every 2 months.	This will allow the team to deliver the analysis if required for regulatory purposes. Interim analyses are no longer needed every 2 months as Substudy A has been unblinded.
Section 10.9.6.2.2 – Blinding of the Sponsor for Substudy C	Updated timing for unblinding of the participant to 3 months after study vaccination administration.	This will allow for collection of blinded safety data up to 3 months after study vaccine administration.
Section 10.9.8.4.3 – Study Assessments and Procedures, Visit 303 for Substudy C	Removed text stating that the participant would be unblinded at the 1-month after booster vaccination visit.	Participants will now be unblinded at 3 months after study vaccine administration.
Section 10.9.9.5 – Sample Size Determination for Substudy C	Updated the assumed response rate for each comparative group at the comparative time point from 90% to 95%.	This was a typo in the previous version of the protocol.
Section 10.10.1.2.1 Schema for Cohorts 1 and 2 in Substudy D	Addition of the PBMC and HLA sample collections.	To provide further clarity on all blood sample collections to be performed during the study.
Section 10.10.1.2.2 Schema for Cohort 3 in Substudy D	Addition of the PBMC and HLA sample collections.	To provide further clarity on all blood sample collections to be performed during the study.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.1.2.1 – Participants in Cohorts 1 and 2 for Substudy D	Addition of Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 10.10.2.1 – Study Rationale for Substudy D	Addition of description of Group 2b (1 dose of BNT162b2).	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 10.10.3 – Objectives, Estimands, and Endpoints for Substudy D	Addition of objectives, estimands, and endpoints for Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 10.10.4.1 – Overall Design for Substudy D	Addition of description of Group 2b (1 dose of BNT162b2), updated total number of participants to 1420, updated Cohort 1 participant total to 615, and updated the table to include Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 10.10.6.2.2 – Blinding of the Sponsor for Substudy D	Updated timing of participant unblinding for Cohort 2 from Visit 402 to Visit 404 and added that Cohort 1 (Groups 1 and 2b) may also be unblinded at this time.	This will allow for collection of blinded safety data up to 3 months after study vaccine administration. Cohort 1 was added to account for Group 2b being added.
Section 10.10.8.2 – Immunogenicity for Substudy D	Addition of text clarifying that B-cell responses will also be tested.	Testing for B-cell responses was planned but was erroneously not specified in the previous protocol version.
Section 10.10.8.6.1.2 – Visit 402 for Substudy D	Moved the text from Visit 402 to Visit 404 describing unblinding of participants in Cohort 2 and added that Cohort 1 (Groups 1 and 2b) may also be unblinded at this time.	This will allow for collection of blinded safety data up to 3 months after study vaccine administration. Cohort 1 was added to account for Group 2b being added.
Section 10.10.9 – Statistical Considerations for Substudy D	Addition of statistical considerations throughout this section related to Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 10.10.9.5 – Sample Size Determination for Substudy D	Updated the assumed response rate for each comparative group at the comparative time point from 90% to 95%.	This was a typographical error in the previous version of the protocol.
Section 10.11 – Appendix 11: Substudy E	Addition of Substudy E.	Substudy E has been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.

Section # and Name	Description of Change	Brief Rationale
Section 10.12 – Appendix 12: Substudy F	Addition of Substudy F.	Substudy F has been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.

Amendment 4 (22 Dec 2021)

Overall Rationale for the Amendment:

- On 26 November 2021 and 30 November 2021, the WHO and the US, respectively, classified a new SARS-CoV-2 variant, B.1.1.529, a VOC, and named it Omicron. Pfizer has developed a new vaccine, BNT162b2 OMICRON (B.1.1.529) (referred to throughout the protocol as BNT162b2 OMI), which is a BNT162b2 RNA-LNP vaccine utilizing modified RNA and encoding the P2 S containing Omicron B.1.1.529 variant-specific mutations. Substudy D has been designed to assess the safety, tolerability, and immunogenicity of BNT162b2 OMI.

Section # and Name	Description of Change	Brief Rationale
Sections 1 through 9	Cross-reference to sections within Substudy D added where required throughout	Substudy D has been added because of the emergence of the new VOC, Omicron
Section 1.1 - Synopsis, Rationale	Addition of details on current VOCs	Substudy D has been added because of the emergence of the new VOC, Omicron
Section 1.1 - Synopsis, Overall Design	Addition of design of Substudy D and number of participants	Substudy D has been added because of the emergence of the new VOC, Omicron
Section 1.1 - Synopsis, Substudy B Design	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 1.1 - Synopsis, Substudy C Design	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 2.2 – Background	Addition of Substudy D	Substudy D has been added because of the emergence of the new VOC, Omicron
Section 2.2.1 - Clinical Overview	Details of EUA for a booster dose in the US, EU, and other countries as well as details of the interim safety and efficacy analysis results for C4591031 Substudy A	This change has been implemented to reflect current recommendations and to provide details of the recent

Section # and Name	Description of Change	Brief Rationale
		interim safety and efficacy analysis results for C4591031 Substudy A
Section 6.6 - Continued Access to Study Intervention After the End of the Study	Confirmation that if the 10-µg dose is found to have a suboptimal immune response, as determined by the sponsor, this group will be offered a single 30-µg dose	To ensure that participants are vaccinated with the currently approved dose and details can be entered on their vaccination records (eg, CDC card)
Section 8.1.1 - Biological Samples	Added detail that no testing of the participants' genetic testing is performed, with the exception of those participants who have provided specific consent to genetic testing samples of the blood for PBMC isolation and HLA typing	Inclusion of PBMC and HLA testing in Substudy D
Section 8.2.4.2 - Local Reactions	Confirming that a reaction classified as Grade 4 should be reported as an AE in the CRF	A confirmed Grade 4 reaction should be reported as an AE in the CRF
Section 8.3.1 - Time Period and Frequency for Collecting AE and SAE Information	Confirmation of the safety reporting time periods for Substudy D	Substudy D has been added because of the emergence of the new VOC, Omicron
Section 10.7.8.5.8.3 - Visit 103	Removal of the request to contact the site for any medically attended events or respiratory symptoms after the final visit	To remove bullets entered in error
Section 10.8.1.2 - Schema	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.8.1.3 - Schedule of Activities for Substudy B	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.8.2.1 - Study Rationale	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.8.4.1 - Overall Design	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.8.5.1 - Inclusion Criteria	Updated the inclusion window for 12- to 17-year-olds from 365 days to 240 days after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron

Section # and Name	Description of Change	Brief Rationale
Section 10.8.8.3.1 - Visit 201 – Vaccination (Day 1)	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Sections 10.8.8.3.7 and 10.9.8.5.1- Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction	Deletion of the temperature reference in the sections to ensure consistency with Section 8.2.4.4	To ensure consistency within the protocol
Section 10.9.1.2 - Schema	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.9.1.3 - Schedule of Activities for Substudy C	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.9.2.1 - Study Rationale	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.9.3 - Objectives, Estimands, and Endpoints	Added an exploratory objective to describe the immune response to VOCs with an endpoint of SARS-CoV-2 neutralizing titers for VOCs	To examine the breadth of neutralizing titers against VOCs
Section 10.9.4.1 - Overall Design	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron

Section # and Name	Description of Change	Brief Rationale
Section 10.9.5.1 - Inclusion Criteria	Updated the inclusion window for 12- to 17-year-olds from 365 days to 240 days after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.9.8.4.1 - Visit 301 – Vaccination (Day 1)	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.9.6.2.2 - Blinding of the Sponsor	Clarification that once a participant has completed their 1-month visit, they may be unblinded to confirm the dose of BNT162b2 received. The study team will also become unblinded to the participant's original study intervention allocation at this time	If the 10-µg dose is found to have a suboptimal immune response, as determined by the sponsor, this group will be offered a single 30-µg dose to ensure that the participant is vaccinated with the currently approved dose and details can be entered on their vaccination records (eg, CDC card)
Section 10.9.8.4.3 - Visit 303	Clarification that once a participant has completed their 1-month visit, they may be unblinded to confirm the dose of BNT162b2 received. The study team will also become unblinded to the participant's original study intervention allocation at this time	If the 10-µg dose is found to have a suboptimal immune response, as determined by the sponsor, this group will be offered a single 30-µg dose to ensure that the participant is vaccinated with the currently approved dose and details can be entered on their vaccination records (eg, CDC card)
Section 10.9.8.5 - Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis	Deletion of reference to troponin blood samples collected during the study	These samples are not collected as part of Substudy C
Section 10.9.9.3.4 - Exploratory Endpoint(s) Analysis	Addition of an exploratory immunogenicity objective	To examine the breadth of neutralizing titers against VOCs in the 2 dose levels
Section 10.10 - Substudy D	Addition of Substudy D	Newly included substudy

Amendment 3 (28 Oct 2021)

Overall Rationale for the Amendment:

- Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Substudy B is added to assess the safety and tolerability of a booster (third) dose of BNT162b2 through the potential analysis of serum troponin levels.

- Substudy C is added to evaluate the safety, tolerability, and immunogenicity of a booster (third) dose of BNT162b2 at 10 µg and at 30 µg. The key objective of the study is to demonstrate that the immune response induced by a booster (third) dose of BNT162b2 at a 10-µg dose is noninferior to the immune response elicited 1 month after the second dose of BNT162b2 at 30 µg (ie, having completed a 2-dose primary series of BNT162b2 [30-µg doses]).

Section # and Name	Description of Change	Brief Rationale
Sections 1 through Section 9	Cross-reference to sections within Substudy B and Substudy C added where required throughout	Substudy B and Substudy C have been added in response to commitments made to CBER
Section 1.1 - Synopsis	Addition of design of Substudy B and Substudy C, number of participants, and use of a DMC (Substudy C only)	Substudy B and Substudy C have been added in response to commitments made to CBER
Section 2 - Introduction and Section 2.2 - Background	Addition of text reporting that BNT162b2 has been fully licensed for use in individuals 16 years of age and above in the US as of 23 Aug 2021	This change has been implemented to reflect current recommendations
Section 2.2 - Background	Addition of Substudy B and Substudy C	Substudy B and Substudy C have been added in response to commitments made to CBER
Sections 5.1 and 5.2 - Inclusion and Exclusion Criteria	Addition of inclusion and exclusion criteria specific to Substudy B and Substudy C	Substudy B and Substudy C have been added in response to commitments made to CBER
Section 7.2 - Participation Discontinuation/ Withdrawal From Study	Confirmation that receipt of a nonstudy COVID vaccine during study participation will result in study withdrawal	This update was implemented to clarify participant withdrawal criteria
Section 7.2.1 - Withdrawal of Consent	Addition of text to confirm that if a participant wishes to receive a COVID-19 vaccine outside of the study, he or she may request to know which study intervention he or she received without needing to reconsent	This update was implemented to allow participants to be unblinded if they want to receive a COVID-19 vaccine outside of the study
Section 8.2.4 - Electronic Diary - Applicable Only to Substudy B and Substudy C	Addition of details for reactogenicity e-diary use	This section was added to describe the use of a reactogenicity e-diary for substudies that will utilize one
Section 8.3.1 - Time Period and Frequency for Collecting AE and SAE Information	Confirmation of the safety reporting time periods for Substudy B and Substudy C	Substudy B and Substudy C have been added in response to commitments made to CBER
Section 8.3.5.1 - Exposure During Pregnancy	Confirmed that any pregnancy that occurs 28 days after the last dose of study intervention will not be considered EDP for this study	This change has been implemented to align with contraception requirements
Section 10.8 - Substudy B	Addition of Substudy B	Newly included substudy
Section 10.9 - Substudy C	Addition of Substudy C	Newly included substudy

Amendment 2 (27 Aug 2021)

Overall Rationale for the Amendment:

- Addition of procedures for monitoring potential myocarditis or pericarditis in response to commitments made to CBER and administrative updates.
- Addition of wording that participants randomized to receive placebo at the booster dose vaccination visit may be offered the opportunity to receive BNT162b2 at a determined time frame at the discretion of the sponsor.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis	Addition of wording on the timing of providing booster doses to placebo participants	This update was implemented to clarify the timing of booster vaccination for placebo participants
Section 2.3.1 – Risk Assessment	Addition of myocarditis and pericarditis	This update has been implemented in response to commitments made to CBER
Section 5 – Study Population	Addition of wording on diversity of recruitment	This addition was implemented for the collection of race and ethnicity data in prescreeners to reflect the enrollment of a diverse participant population
Section 5.2 – Exclusion Criteria	Exclusion criterion 13 edited to change the exclusion timeframe from the duration of study participation to within 28 days of confirmed receipt of BNT162b2	This criterion was changed to allow study participants to enroll in other clinical trials before the end of their study participation
Section 8.2.5– Pregnancy Testing	Clarified the timing of pregnancy tests	This update addresses discrepancies with SoA
Section 8.3.8 – Adverse Events of Special Interest	Addition of myocarditis and pericarditis	This update has been implemented in response to commitments made to CBER
Section 10.1.3 – Informed Consent Process	Clarified that assent must be obtained when the participant has the capacity to provide assent	This update has been made to ensure compliance with IRB./ECs
Section 10.7.1.3.1 – Administration of BNT162b2 to Those Originally Assigned to Placebo	Addition of wording on the timing of providing booster doses to placebo participants	This update was implemented to clarify the timing of booster vaccination for placebo participants
Section 10.7.4.1 – Overall Design	Addition of wording on the timing of providing booster doses to placebo participants	This update was implemented to clarify the timing of booster vaccination for placebo participants
Section 10.7.6.2.1 – Blinding of Site Personnel	Addition of wording on unblinding decisions	This addition was implemented to allow the sponsor to be unblinded outside of the interim analyses
Section 10.7.6.2.2 – Blinding of the Sponsor	Addition of wording on unblinding decisions	This addition was implemented to allow the sponsor to be unblinded outside of the interim analyses

Section # and Name	Description of Change	Brief Rationale
Section 10.7.8.5 – Study Procedures	Addition of a procedure to any visit that occurs sooner than 1 month after any vaccination	This update has been implemented in response to commitments made to CBER
Section 10.7.8.5.1 – Visit 1 – Booster Vaccination (Day 1)	Clarified wording on site staff roles in relation to randomization and study intervention allocation number assignment	This update has been made to ensure the blind is maintained by the investigator site staff
Section 10.7.8.5.8 – Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo	Addition of wording on the timing of providing booster doses to placebo participants	This update was implemented to clarify the timing of booster vaccination for placebo participants
Section 10.7.8.5.9 – Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis	Addition of an unplanned visit to capture data pertaining to myocarditis and pericarditis	This visit has been implemented in response to commitments made to CBER
Section 10.8 – Appendix 8: Protocol Amendment History	Addition of Appendix 8 to include the protocol amendment history, and moved the Protocol Amendment Summary of Changes Table for protocol amendment 1 from the beginning of the document to this new section	This update has been made to ensure only the latest Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents

Amendment 1 (27 May 2021)

Overall Rationale for the Amendment: Correction to exclusion criterion and administrative update.

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Removal of exclusion criterion 9: Previous participation in other studies involving study intervention containing LNPs.	Included in the original protocol in error. C4591031 Substudy A aims to enroll participants having previously received BNT162b2 in Study C4591001.
5.2. Exclusion Criteria	Addition of new exclusion criterion (Number 9) to exclude participants having previously received a COVID-19 vaccine other than BNT162b2.	To exclude participants who have received anything more than 2 doses of only BNT162b2 COVID-19 vaccine.
10.7.4.1. Overall Design	Update to cutoff values for age strata from ≥ 16 to < 55 and ≥ 55 years of age to ≥ 16 to 55 and > 55 years of age.	To ensure the age strata match those used in Study C4591001.
10.7.9.5. Sample Size Determination	Update to the expected number of cases in Table 1 from 97 to 98 at 7 days to 6 months if nonboosted and $IR0 = 0.14/\text{pyr}$.	To address prior rounding error.

10.14. Appendix 14: Abbreviations

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

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCR	B-cell receptor
β-hCG	beta-human chorionic gonadotropin
BNT162b2 OMI	BNT162b2 OMICRON (B.1.1.529)
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatinine kinase
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
E1, E2, E3, E4	Estimand 1, Estimand 2, Estimand 3, Estimand 4
e-diary	electronic diary
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration

Abbreviation	Term
FiO ₂	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
IgA	Immunoglobulin A
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	independent review committee
IRT	interactive response technology
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

Abbreviation	Term
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
NIMP	noninvestigational medicinal product
OMI	Omicron (ie, in BNT162b2 OMI)
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PACL	protocol administrative change letter
PaO ₂	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
QTL	quality tolerance limit
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S	spike protein
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO ₂	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SSD	Substudy D
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TCR	T-cell receptor
UK	United Kingdom
ULN	upper limit of normal
US	United States
VAED	vaccine-associated enhanced disease
VE	vaccine efficacy
VOC	variant of concern
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

10.15. Appendix 15: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

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

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm³ within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

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

Known HBV infection

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

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

10.16. Appendix 16: Genetics

Use/Analysis of DNA and/or RNA

- Genetic variation may impact a participant's response to study intervention, as well as 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 a 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 10.10.8.5](#) and [Section 10.11.8.5](#)) 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.

11. REFERENCES

- ¹ GOV.UK. UK medicines regulator gives approval for first UK COVID-19 vaccine. Available from: <https://www.gov.uk/government/news/uk-medicines-regulator-gives-approval-for-first-uk-covid-19-vaccine>. Accessed: 28 Mar 2021.
- ² Food and Drug Administration. Comirnaty and Pfizer-BioNTech COVID-19 vaccine. Available from: <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine>. Accessed: 28 Mar 2021.
- ³ 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>. Accessed: 28 Mar 2021.
- ⁴ McGill COVID19 Vaccine Tracker Team. COVID19 vaccine tracker: Pfizer/BioNTech: BNT162b2. Available from: <https://covid19.trackvaccines.org/vaccines/6/>. Accessed: 28 Mar 2021.
- ⁵ Food and Drug Administration. Comirnaty and Pfizer-BioNTech COVID-19 vaccine. BLA approval letter dated August 23, 2021. Available from: <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine>. Accessed: 26 Oct 2021.
- ⁶ Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html>. Updated: 01 Dec 2021. Accessed: 06 Dec 2021.
- ⁷ 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.
- ⁸ 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>. Accessed: 09 Dec 2021.
- ⁹ Pfizer. Pfizer and BioNTech announce Phase 3 trial data showing high efficacy of a booster dose of their COVID-19 vaccine [press release]. Available from: <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-phase-3-trial-data-showing>. Accessed: 09 Dec 2021.

- ¹⁰ World Health Organization. Timeline: WHO's COVID-19 response. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#!>. Accessed: 30 Apr 2021.
- ¹¹ World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. Available from: [https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-\(covid-2019\)-and-the-virus-that-causes-it](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it). Accessed: 29 Mar 2021.
- ¹² World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020. Available from: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>. Published: 11 Mar 2020. Accessed: 30 Apr 2021.
- ¹³ World Health Organization. Weekly epidemiological update on COVID-19 – 15 March 2022. Available from: <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---15-march-2022>. Accessed: 17 Mar 2022.
- ¹⁴ McGill COVID19 Vaccine Tracker Team. COVID19 vaccine tracker. Available from: <https://covid19.trackvaccines.org/vaccines/>. Accessed: 04 May 2021.
- ¹⁵ Comirnaty [package insert]. BioNTech and Pfizer; August 2021. Available from: <https://www.fda.gov/media/151707/download>. Accessed: 26 Oct 2021.
- ¹⁶ Food and Drug Administration. Emergency use authorization for vaccines to prevent COVID-19. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19>. Published: 22 Feb 2021. Accessed: 29 Mar 2021.
- ¹⁷ Bozkurt B, Colvin M, Cook J, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. *Circulation*. 2016;134(23):e579-e646.
- ¹⁸ Brighton Collaboration. Myocarditis/pericarditis case definition. Available from: <https://brightoncollaboration.us/myocarditis-case-definition-update/>. Accessed: 20 Jul 2021.
- ¹⁹ Daniels CJ, Rajpal S, Greenshields JT, et al. Prevalence of clinical and subclinical myocarditis in competitive athletes with recent SARS-CoV-2 infection: results from the Big Ten COVID-19 Cardiac Registry. *JAMA Cardiol*. 2021;6(9):1078-87.

- 20 Pfizer and BioNTech. Vaccines and Related Biological Products Advisory Committee Meeting, September 17, 2021. FDA briefing document: BNT162b2 [COMIRNATY (COVID-19 vaccine, mRNA)]. Food and Drug Administration website. Available from: <https://www.fda.gov/media/152161/download>. Accessed: 18 Dec 2021.
- 21 Frenck RW Jr, Klein NP, Kitchin N, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med*. 2021;385(3):239-50.
- 22 LKS Faculty of Medicine at the University of Hong Kong. HKUMed finds Omicron SARS-CoV-2 can infect faster and better than Delta in human bronchus but with less severe infection in lung. Available from: <https://www.med.hku.hk/en/news/press/20211215-omicron-sars-cov-2-infection>. Published: 15 Dec 2021. Accessed: 12 Jan 2022.
- 23 Centers for Disease Control and Prevention. Science brief: Omicron (B.1.1.529) variant. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html>. Updated: 02 Dec 2021. Accessed: 06 Dec 2021.
- 24 Pfizer. Pfizer and BioNTech provide update on Omicron variant [press release]. Available from: <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant>. Accessed: 09 Dec 2021.
- 25 Centers for Disease Control and Prevention. COVID data tracker: variant proportions. Available from: <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>. Accessed: 16 Jan 2022.
- 26 UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1044481/Technical-Briefing-31-Dec-2021-Omicron_severity_update.pdf. Accessed: 07 Jan 2022.
- 27 Nemet I, Kliker L, Lustig Y, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 omicron infection. *N Engl J Med*. 2021 Dec 29. doi: 10.1056/NEJMc2119358. Epub ahead of print.
- 28 Pfizer and BioNTech. FDA briefing document: Pfizer-BioNTech COVID-19 vaccine. Available from: <https://www.fda.gov/media/144245/download>. Accessed: 30 Apr 2021.

- ²⁹ 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>. Accessed: 27 Apr 2021.
- ³⁰ Food and Drug Administration. FDA authorizes booster dose of Pfizer-BioNTech COVID-19 vaccine for certain populations. Available from: <https://www.fda.gov/news-events/press-announcements/fda-authorizes-booster-dose-pfizer-biontech-covid-19-vaccine-certain-populations>. Accessed: 19 Dec 2021.
- ³¹ Pfizer. Pfizer and BioNTech receive expanded U.S. FDA emergency use authorization of COVID-19 vaccine booster to include individuals 18 and older [press release]. Available from: <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-receive-expanded-us-fda-emergency-use>. Accessed: 19 Dec 2021.
- ³² Food and Drug Administration. Coronavirus (COVID-19) update: FDA expands eligibility for Pfizer-BioNTech COVID-19 booster dose to 16- and 17-year-olds. Available from: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-pfizer-biontech-covid-19-booster-dose-16-and-17>. Accessed: 19 Dec 2021.
- ³³ Pfizer and BioNTech. Pfizer and BioNTech receive CHMP positive opinion for COVID-19 vaccine booster in the European Union [press release]. Available from: https://cdn.pfizer.com/pfizercom/2021-10/COVID19_Booster_CHMP_Opinion_FINAL.pdf. Accessed: 20 Dec 2021.
- ³⁴ Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against COVID-19 in Israel. *N Engl J Med*. 2021;385(15):1393-400.
- ³⁵ 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.
- ³⁶ 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.
- ³⁷ Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T_H1T cell responses. *Nature*. 2020;586(7830):594-9.
- ³⁸ Mulligan MJ, Lyke KE, Kitchin N, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature*. 2020;586(7830):589-93.

- ³⁹ 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.
- ⁴⁰ Pfizer. About our landmark trial. Available from: <https://www.pfizer.com/science/coronavirus/vaccine/about-our-landmark-trial>. Accessed: 27 Apr 2021.
- ⁴¹ Food and Drug Administration. Development and licensure of vaccines to prevent COVID-19. Guidance for industry. Available from: <https://www.fda.gov/media/139638/download>. Accessed: 27 Apr 2021.
- ⁴² Centers for Disease Control and Prevention. People with certain medical conditions. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Accessed: 27 Apr 2021.
- ⁴³ Agresti A, Min Y. Simple improved confidence intervals for comparing matched proportions. *Stat Med*. 2005;24(5):729-40.
- ⁴⁴ Centers for Disease Control and Prevention. Science brief: Omicron (B.1.1.529) variant. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html>. Accessed: 17 Dec 2021.
- ⁴⁵ Food and Drug Administration. Development and licensure of vaccines to prevent COVID-19. Guidance for industry. Available from: <https://www.fda.gov/media/139638/download>. Accessed: 27 Apr 2021.
- ⁴⁶ Centers for Disease Control and Prevention. People with certain medical conditions. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Accessed: 27 Apr 2021.

Document Approval Record

Document Name:

C4591031 Clinical Protocol Amendment 12 Clean Copy, 20 SEP 2023

Document Title:

A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF BNT162b2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH BNT162b2

Signed By:

Date(GMT)

Signing Capacity

PPD

20-Sep-2023 17:32:11

Final Approval

PPD

20-Sep-2023 21:23:33

Final Approval