A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

TABLE OF CONTENTS

LIST OF TABLES 8
1. PROTOCOL SUMMARY 9
1.1. Synopsis 9
1.2. Schema 17
1.3. Schedule of Activities 18
1.3.1. Phase 1 18
1.3.2. Phase 2/3 23
2. INTRODUCTION 26
2.1. Study Rationale 26
2.2. Background 26
2.2.1. Clinical Overview 27
2.3. Benefit/Risk Assessment 27
2.3.1. Risk Assessment 29
2.3.2. Benefit Assessment 31
2.3.3. Overall Benefit/Risk Conclusion 31
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 31
3.1. For Phase 1 31
3.2. For Phase 2/3 33
4. STUDY DESIGN 36
4.1. Overall Design 36
4.1.1. Phase 1 36
4.1.2. Phase 2/3 37
4.2. Scientific Rationale for Study Design 39
4.3. Justification for Dose 39
4.4. End of Study Definition 40
5. STUDY POPULATION 40
5.1. Inclusion Criteria 40
5.2. Exclusion Criteria 41

5.3. Lifestyle Considerations....44
5.3.1. Contraception....44
5.4. Screen Failures....44
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration....44
6. STUDY INTERVENTION....45
6.1. Study Intervention(s) Administered....46
6.1.1. Manufacturing Process....46
6.1.2. Administration....46
6.2. Preparation/Handling/Storage/Accountability....47
6.2.1. Preparation and Dispensing....48
6.3. Measures to Minimize Bias: Randomization and Blinding....48
6.3.1. Allocation to Study Intervention....48
6.3.2. Blinding of Site Personnel....48
6.3.3. Blinding of the Sponsor....49
6.3.4. Breaking the Blind....50
6.4. Study Intervention Compliance....50
6.5. Concomitant Therapy....50
6.5.1. Prohibited During the Study....50
6.5.2. Permitted During the Study....51
6.6. Dose Modification....51
6.7. Intervention After the End of the Study....52
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL....52
7.1. Discontinuation of Study Intervention....52
7.2. Participant Discontinuation/Withdrawal From the Study....53
7.2.1. Withdrawal of Consent....53
7.3. Lost to Follow-up....54
8. STUDY ASSESSMENTS AND PROCEDURES....54
8.1. Efficacy and/or Immunogenicity Assessments....55
8.1.1. Biological Samples....58
8.2. Safety Assessments....58
8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)....59

8.2.2. Electronic Diary 59
8.2.2.1. Grading Scales 60
8.2.2.2. Local Reactions 60
8.2.2.3. Systemic Events 61
8.2.2.4. Fever 62
8.2.2.5. Antipyretic Medication 62
8.2.3. Phase 1 Stopping Rules 62
8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule 64
8.2.5. Randomization and Vaccination After a Stopping Rule Is Met 64
8.2.6. Pregnancy Testing 65
8.3. Adverse Events and Serious Adverse Events 65
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 65
8.3.1.1. Reporting SAEs to Pfizer Safety 66
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF 66
8.3.2. Method of Detecting AEs and SAEs 66
8.3.3. Follow-up of AEs and SAEs 66
8.3.4. Regulatory Reporting Requirements for SAEs 67
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 67
8.3.5.1. Exposure During Pregnancy 67
8.3.5.2. Exposure During Breastfeeding 69
8.3.5.3. Occupational Exposure 69
8.3.6. Cardiovascular and Death Events 70
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 70
8.3.8. Adverse Events of Special Interest 70
8.3.8.1. Lack of Efficacy 70
8.3.9. Medical Device Deficiencies 70
8.3.10. Medication Errors 70
8.4. Treatment of Overdose 71
8.5. Pharmacokinetics 72
8.6. Pharmacodynamics 72

8.7. Genetics 72
8.8. Biomarkers 72
8.9. Immunogenicity Assessments 72
8.10. Health Economics 72
8.11. Study Procedures 72
8.11.1. Phase 1 72
8.11.1.1. Screening: (0 to 28 Days Before Visit 1) 72
8.11.1.2. Visit 1 – Vaccination 1: (Day 1) 74
8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1) 76
8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1) 78
8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1) 79
8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4) 81
8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4) 82
8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4) 83
8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4) 84
8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4) 84
8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4) 85
8.11.2. Phase 2/3 85
8.11.2.1. Visit 1 – Vaccination 1: (Day 1) 85
8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1) 88
8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2) 90
8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2) 91
8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2) 91
8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2) 92

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction 92
8.13. COVID-19 Surveillance (All Participants) 93
8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset) 95
8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit) 96
8.14. Communication and Use of Technology 96
8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits 97
9. STATISTICAL CONSIDERATIONS 98
9.1. Estimands and Statistical Hypotheses 98
9.1.1. Estimands 98
9.1.2. Statistical Hypotheses 99
9.1.2.1. Statistical Hypothesis Evaluation for Efficacy 99
9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity 99
9.2. Sample Size Determination 99
9.3. Analysis Sets 101
9.4. Statistical Analyses 102
9.4.1. Immunogenicity Analyses 102
9.4.2. Efficacy Analyses 107
9.4.3. Safety Analyses 109
9.4.4. Other Analyses 110
9.5. Interim Analyses 111
9.5.1. Analysis Timing 114
9.6. Data Monitoring Committee or Other Independent Oversight Committee 114
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 116
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 116
10.1.1. Regulatory and Ethical Considerations 116
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 116
10.1.2. Informed Consent Process 117
10.1.3. Data Protection 118

10.1.4. Dissemination of Clinical Study Data 118
10.1.5. Data Quality Assurance 119
10.1.6. Source Documents 120
10.1.7. Study and Site Start and Closure 121
10.1.8. Sponsor's Qualified Medical Personnel 121
10.2. Appendix 2: Clinical Laboratory Tests 123
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 125
10.3.1. Definition of AE 125
10.3.2. Definition of SAE 126
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs....128
10.3.4. Reporting of SAEs 131
10.4. Appendix 4: Contraceptive Guidance 132
10.4.1. Male Participant Reproductive Inclusion Criteria 132
10.4.2. Female Participant Reproductive Inclusion Criteria....132
10.4.3. Woman of Childbearing Potential 133
10.4.4. Contraception Methods....134
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 136
10.6. Appendix 6: Abbreviations 138
10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19 142
10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection 145
11. REFERENCES 146

LIST OF TABLES

Table 1. Local Reaction Grading Scale 60
Table 2. Systemic Event Grading Scale.....61
Table 3. Scale for Fever.....62
Table 4. Power Analysis for Noninferiority Assessment 100
Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes 101
Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility.....112
Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses.....113
Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall.....113
Table 9. Laboratory Abnormality Grading Scale 123
Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S) 143
Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A) 144

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• 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
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in <u>all participants</u> randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: ○ 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)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• 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
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers

Objectives[a]	Estimands	Endpoints
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• All safety endpoints described above • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as $VE = 100 \times (1 - IRR)$, where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90%

power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

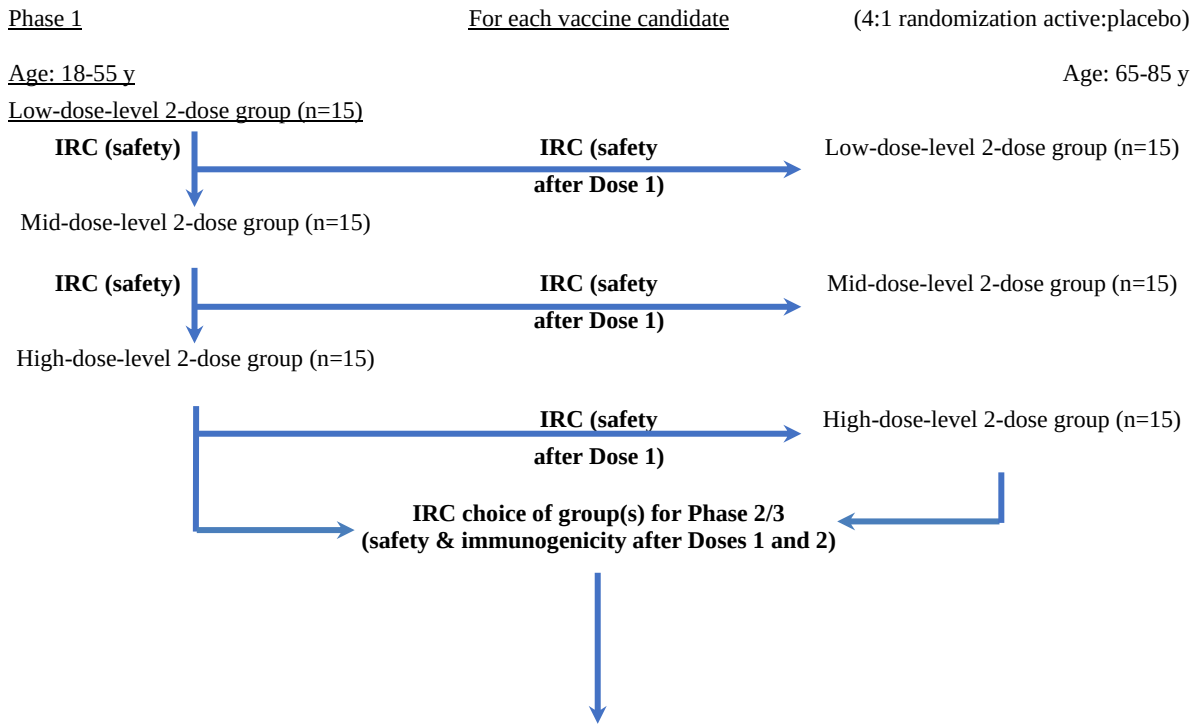
VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objective to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, percentage of participants with ≥ specified threshold, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and/or RBD-binding IgG levels at the various time points.

1.2. Schema



Abbreviation: IRC = internal review committee.

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.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~20 mL	~20 mL	~20 mL		~20 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		◄	———	►	◄	►							
Review ongoing reactogenicity e-diary					X		X						

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
symptoms and obtain stop dates													
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	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	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					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain 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 (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄—►	◄—►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
Collect e-diary or assist the participant to delete application						X		

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. 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.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a

participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see Section 8.2.2).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.

- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.

- All participants 12 to 15 years of age will be included in the reactogenicity subset (see Section 8.2.2).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

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.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
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 would obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• 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 Hematology and chemistry laboratory parameters detailed in Section 10.2

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

Objectives[a]	Estimands	Endpoints
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• All safety endpoints described above • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

This protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to Section 8.3.1.1 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)

- Controlled enrollment (required only for the first candidate and/or dose level studied):
    - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
    - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
    - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
    - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
    - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1,

respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 250 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those

vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50-µg dose level for BNT162b1 and BNT162b2 is removed and the 100-µg dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization. Note that participants <18 years of age cannot be enrolled in the EU.
    - 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 Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Section 10.8.

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

Informed Consent:

5. Capable of giving personal signed informed consent/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.

5.2. Exclusion Criteria

Participants are excluded from the study 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. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

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

4. Receipt of medications intended to prevent COVID-19.

5. 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.

6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - Chronic liver disease
    - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
    - Resident in a long-term facility
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).

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

9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

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

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into

the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

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

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. 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.

5.3. Lifestyle Considerations

5.3.1. Contraception

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). 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 randomly 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 SAE.

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/Study Intervention Administration

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.

1. Current febrile illness (body temperature ≥100.4°F [≥38°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.

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

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

4. 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. STUDY INTERVENTION

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.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled 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 or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

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

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.

6.2. Preparation/Handling/Storage/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.

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 dispensing.

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

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 through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a 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.

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 of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study

intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (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 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

- 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. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

6.3.4. Breaking the Blind

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

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. Concomitant Therapy

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

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. 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 onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after 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 to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or 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.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in Section 6.5.1 required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see Section 6.5.1), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, due to a medication error, a participant receives 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa), the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. In this situation:

- Obtain informed consent for administration of the additional dose.

- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- 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.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

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

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 (definitive discontinuation). Reasons for definitive discontinuation of study intervention may 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). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms does not meet exclusion criterion 5 and should not result in discontinuation of study intervention, whereas a COVID-19 diagnosis does meet exclusion criterion 5 and should result in discontinuation of study intervention (see Section 8.15).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, 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 may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

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.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

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.

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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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

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

The full 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.

The total blood sampling volume for individual participants in this study is approximately up to: 515 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum. Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. 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.

8.1. Efficacy and/or Immunogenicity Assessments

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 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] 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 a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) 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)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (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.

  The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

    - Fatigue;
    - Headache;
    - Nasal congestion or runny nose;
    - Nausea.
- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

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

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

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay
- S1-binding IgG level assay
- RBD-binding IgG level assay
- N-binding antibody assay

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

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. 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 products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that 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 DNA is performed.

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 his/her 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 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See Appendix 2 for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant’s own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant’s experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

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

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

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

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

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

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

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

8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

8.2.2.4. 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 ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

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

Table 3. Scale for Fever

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

8.2.2.5. Antipyretic Medication

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

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see Section 8.2.2) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.2.2.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. 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 and Serious Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

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).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/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 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each 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 approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 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 and Pfizer concurs with that assessment.

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

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

If a participant definitively 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 Report Form.

Investigators are not obligated to actively seek 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 Report 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 Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of 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/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 towards 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. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure 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 exposure during pregnancy:
    - 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 Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and 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 Report Form is maintained in the investigator site file.

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

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

- Spontaneous abortion including miscarriage and missed abortion;

- 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 Report 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 Report 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

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

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

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.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy 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 Report 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 Report Form **only when associated with an SAE.**

8.4. 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 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.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

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

8.11. Study Procedures

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 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; however, the visit can occur over more than 1 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.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- 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. AEs that occur prior to dosing should be noted on the Medical History CRF.
- 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 8.13.
- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

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.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- 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.

- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, 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 measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.14), 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 e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to 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 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant 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 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant 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 8.13.
- 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.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant 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 8.13.
- 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.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

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.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention

but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

- 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 hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- 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.
- 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 his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant 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 8.13.

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

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

- Fever ≥39.0°C (≥102.1°F).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- 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.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- 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.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- 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 8.13.

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity 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 he or she experiences any respiratory symptoms as detailed in Section 8.13.
- 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.

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- 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 8.13.
- 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.

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- 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.

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – 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 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 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 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 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- 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 participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- 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.
- For participants in the reactogenicity subset, 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.

- For participants not in the reactogenicity subset, 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 8.14), 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.

    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

    - For all participants, 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 8.14 for further details.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

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

    - Severe pain at the injection site.

    - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, 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 he or she experiences any respiratory symptoms as detailed in Section 8.13.

- 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.

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

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

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.
- If the participant is part of the reactogenicity subset, 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 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 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 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.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- 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.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, 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 8.13.

- 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.

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

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, 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 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 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 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- 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 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- 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 a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 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 8.3.
- 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.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 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 4 (if any).
- 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 8.13.
- 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.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 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 5 (if any).
- 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.

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

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) 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 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) 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 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- 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.

8.13. COVID-19 Surveillance (All 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). 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 (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) 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.

- 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.

8.13.1. 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 obtain the following information:

- 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 6.5.1 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 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 ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)

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

        - Significant acute renal, hepatic, or neurologic dysfunction

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

    - Clinical diagnosis

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

  - Full blood count
  - Blood chemistry, specifically creatinine, urea, liver function tests, 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
- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

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

- 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 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- 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.

8.14. 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; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or 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.

8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits

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

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) 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 2 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.

Participants who have a positive SARS-CoV-2 NAAT result prior to Visit 2 should be handled as follows:

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 5; therefore, Vaccination 2 should proceed as normal.

- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): This meets exclusion criterion 5; therefore, Vaccination 2 should not be given but the participant should remain in the study.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (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. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). 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 also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being

nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 250 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.623	-0.2	200	90.8%

Abbreviation: GMR = geometric mean ratio.

a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 1, N=12). Calculation may be updated if additional information becomes available to better estimate the standard deviation.

b. At 0.05 alpha level (2-sided).

For safety outcomes, Table 5 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 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.

Population	Description
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available 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.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 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 natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-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. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of

Endpoint	Statistical Analysis Methods
	participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) 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. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and

Endpoint	Statistical Analysis Methods
16- to 25-year age group)	2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination 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 natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3:

Endpoint	Statistical Analysis Methods
	• 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-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. **Percentage of participants with antibody levels ≥ predefined threshold(s) for SARS-CoV-2 serological parameters** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels and/or RBD-binding IgG levels, N-binding antibody, and SARS-CoV-2 detection by NAAT, percentages (and 2-sided 95% CIs) of participants with antibody levels ≥ predefined threshold(s) will be provided for each investigational product within each group at baseline and each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination The Clopper-Pearson method will be used to calculate the CIs. **Percentage of participants with the immune response (non-S) to SARS-CoV-2 for N-binding antibody at the time points when data are available** The Clopper-Pearson method will be used to calculate the CIs. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

Endpoint	Statistical Analysis Methods
	RCDCs for immunogenicity results Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population.

Endpoint	Statistical Analysis Methods
	The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the**

Endpoint	Statistical Analysis Methods
	second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each 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. For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. 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

Endpoint	Statistical Analysis Methods
	review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected randomly for the analysis.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall Type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

9.5.1. Analysis Timing

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

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.
- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. 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 in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met

- Review of safety and/or immunogenicity data to:
  - Allow groups of participants of 65 to 85 years of age to proceed
  - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
  - Whether any groups may not be started
  - Whether any groups may be terminated early
  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

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 completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 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.

Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

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 and 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.

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 guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (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 ICH GCP that the investigator becomes aware of.

10.1.2. Informed Consent Process

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

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

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

The participant must be informed that his/her 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 or her parent(s)/legal guardian 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 the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. 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 identification. 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.

10.1.4. 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 available data from these trials 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.

10.1.5. 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.

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

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.

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 (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, remote, or on-site monitoring), are provided in the monitoring plan.

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

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, and all applicable regulatory requirements.

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

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

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

10.1.6. 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 can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. 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 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 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.

10.1.8. 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.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

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

10.3.1. Definition of AE

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

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions 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/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 which 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 SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
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 detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

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

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

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/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/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/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/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/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/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 Report 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 completed CRF.

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

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse 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 a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- 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:

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

    - 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.

3. Postmenopausal female:

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

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

        - 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.

5. Vasectomized partner:

    - 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;

    - Injectable.

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 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

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

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × 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 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** 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 × ULN; or >8 × 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 × ULN **or** if the value reaches >3 × 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 cases of Hy's law, 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, 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 and 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: Abbreviations

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

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
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
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
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
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation	Term
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
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	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MAR	missing at random
MCH	mean corpuscular hemoglobin

Abbreviation	Term
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
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
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
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
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination

Abbreviation	Term
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

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

Known HIV infection

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

Known HCV infection

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

Known HBV infection

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

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

11. REFERENCES

1 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. 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: 01 Apr 2020.

2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 70. In: Data as reported by national authorities by 10:00 CET 30 March 2020. Geneva, Switzerland: World Health Organization; 2020.

3 Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.

4 Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. Front Immunol 2018;9:1963.

5 Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov 2014;13(10):759-80.

6 BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.

7 Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37(25):3326-34.

8 US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

9 Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

10 Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.