Title Page

AN INTERVENTIONAL EFFICACY AND SAFETY, PHASE 2, RANDOMIZED, DOUBLE-BLIND, 3-ARM STUDY TO INVESTIGATE NIRMATRELVIR/RITONAVIR IN NONHOSPITALIZED PARTICIPANTS AT LEAST 12 YEARS OF AGE WITH SYMPTOMATIC COVID-19 WHO ARE IMMUNOCOMPROMISED

Study Intervention Number:	PF-07321332
Study Intervention Name:	nirmatrelvir
US IND Number:	153517
EudraCT/CTIS Number:	2022-001362-35
ClinicalTrials.gov ID:	NCT05438602
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4671034
Phase:	2

Brief Title:

A Study to Learn About the Study Medicines Called Nirmatrelvir/Ritonavir in People at Least 12 Years of Age With COVID-19 Who Are Immunocompromised

Document History

Document	Version Date
Amendment 1	13 September 2022
Original protocol	27 May 2022

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

Protocol Amendment Summary of Changes Table

Amendment 1 (13 September 2022):

Overall Rationale for the Amendment: This protocol was amended based on regulatory feedback to update the primary analysis and include an additional population of nonhospitalized symptomatic participants who are immunocompromised with a rebound in COVID-19.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
1.1 Synopsis 3.0 Objectives, Endpoints, and Estimands 9.1.1.1 Primary Estimand/Coprimary Estimands	Revised estimand to include patients who received non-study antiviral or monoclonal antibody therapy as not achieving the primary endpoint.	To address regulatory feedback recommending a more conservative approach and considering patients who received non-study antiviral or monoclonal antibody therapy as a failure in the primary analysis.	substantial
1.1 Synopsis 3.0 Objectives, Endpoints, and Estimands 9.1.1.1 Primary Estimand/Coprimary Estimands 9.3.2.1 Definitions of Endpoint(s) 9.3.2.2 Main Analytical Approach 9.5 Sample Size Determination	For the primary endpoint, changed the beginning of the sustained period from “the end of active treatment” to “Day 15”.	To address regulatory feedback recommending a standard follow-up period duration for all treatment groups for the primary endpoint.	substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
9.3.2.1 Definition of Endpoint(s)	Revised sustained definition for the primary endpoint NP swab SARS-CoV-2 RNA level from "not ≥2.5 $\log_{10}$ copies/mL" to "not ≥2.0 $\log_{10}$ copies/mL" at any study visit (through Day 44) following the first study visit where the participant's NP swab SARS-CoV-2 RNA <LLOQ.	To address regulatory feedback recommending modification to the definition of sustained.	substantial
9.3.2.3 Supplementary Analysis/Analyses	Revised supplementary analysis for the primary endpoint to exclude data after the date of nonstudy antiviral or monoclonal antibody start for participants who received non-study antiviral or monoclonal antibody therapy.	To address regulatory feedback by designating this as a supplemental analysis instead of primary analysis.	substantial
1.1 Synopsis 2.1 Study Rationale 4.1 Overall Design 4.2 Scientific Rationale for Study Design	Added an additional population of participants to the study who are immunocompromised with COVID-19 rebound within 14 days following completion of an initial 5-day nirmatrelvir/ritonavir treatment course.	To address regulatory feedback by adding this population to the study.	substantial
1.1 Synopsis 5.1 Inclusion Criteria 10.9.5 Inclusion Criteria for Additional Population With COVID-19 Rebound	Added Inclusion Criterion #5 that allows participants who are immunocompromised and have COVID-19 rebound to enroll in the study; and added Section 10.9.5 that further describes inclusion criteria for the additional population with COVID-19 rebound.	To address regulatory feedback pertaining to the importance of studying rebound as a separate group of immunocompromised patients previously treated with a 5-day course of PAXLOVID.	substantial
1.1 Synopsis 5.1 Inclusion Criteria	Revised Inclusion Criterion #2 to specify participants with COVID-19 rebound must have confirmed SARS-CoV-2 infection as specified in Appendix 9, Section 10.9.2 for the main study population or Appendix 9, Section 10.9.5 for the additional population with rebound.	To address regulatory feedback pertaining to the importance of studying rebound as a separate group of immunocompromised	substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
10.9.2 Confirm SARS-CoV-2 Infection Details for the Main Study Population 10.9.5 Inclusion Criteria for Additional Population With COVID-19 Rebound		patients previously treated with a 5-day course of PAXLOVID and establishing specific inclusion criteria for this group.	
Synopsis 1.1 4.1 Overall Design 6.3 Assignment to Study Intervention	Added that enrollment of participants considered immunocompromised based solely on receiving corticosteroids or TNF blockers in the additional population with rebound will not be capped or stratified.	To clarify enrollment of participants in the additional population with rebound.	substantial
6.9 Prior and Concomitant Therapy 10.9.7 Prior/Concomitant Therapy	Added prior therapy of a 5-day nirmatrelvir/ritonavir course for participants in the additional population with rebound is required and not prohibited.	To be consistent with eligibility criteria.	substantial
8.5 Pharmacokinetics	Clarified that 1 mL of blood is needed for measurement of nirmatrelvir and ritonavir.	To clarify total blood volume so that extra blood is not needlessly drawn.	substantial
10.8 Prohibited Concomitant Medications That May Result in DDI	Text describing Tables 4 and 5 was revised to clarify DDI table content. Tables were updated with information from the Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid (August 2022).	Updates to the list of precautionary and prohibited medications.	substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Cover page and 1.1 Synopsis	Added NCT number.	To incorporate changes from the 12 July 2022 PACL.	nonsubstantial
1.1 Synopsis	Revised the definition of enrolled to include those who complete informed consent/assent and screening.	To clarify that potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled. To incorporate changes from the 12 July 2022 PACL.	nonsubstantial
1.1 Synopsis 4.1 Overall Design	Added text for the timing of enrollment for the additional population with rebound.	To clarify enrollment of the population with rebound in relation to the main study population.	nonsubstantial
Synopsis 1.1 4.1 Overall Design	Removed autoimmune disorder treatment for sole reason why enrolled participants receive corticosteroids or TNF blockers, which are capped at approximately 25%.	To clarify that participants on corticosteroids or TNF blockers, who are capped at ~25%, is not restricted to only participants treated for autoimmune disorders.	nonsubstantial
1.1 Synopsis 5.2 Exclusion Criteria 6.1 Study Intervention(s) Administered 6.1.1 Administration 6.6 Dose Modification 7.1 Discontinuation	Updated units for eGFR as mL/min/1.73m^2 and units for CrCl as mL/min. in these sections.	Updated for consistency.	nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
of Study Intervention			
1.1 Synopsis 9.1.1.1 Primary Estimand/Coprimary Estimands 9.3.2.1 Definition of Endpoint(s) 9.3.2.2 Main Analytical Approach	Clarified data will be analyzed separately for the main study population and the additional population with rebound.	To clarify data analysis.	nonsubstantial
1.1 Synopsis 4.1 Overall Design 9.5 Sample Size Determination	Added that sample size of participants with COVID-19 rebound would be up to 50, and accordingly specified that total sample size of study is up to 200 participants.	To specify maximum sample size of the additional population with rebound and maximum total sample size of study.	nonsubstantial
1.3 Schedule of Activities	Added note for vital status check that secondary contacts may be used. To be consistent with revisions to Inclusion Criterion #2, updated the note for a positive SARS-CoV-2 test obtained within 5 days for the main study population or 24 hours for the population with rebound prior to randomization. Updated the note for the rapid antigen testing to clarify that postbaseline tests will be performed by an HCP. Added cross-reference to Section 8.1.4 for telehealth activities and removed 'telemedicine' from Serious and nonserious AE monitoring notes since telehealth and telemedicine are synonymous.	Updated for consistency with Section 8.1.1.3. To be consistent with Inclusion Criterion #2 and to clarify that postbaseline rapid antigen testing should be performed by an HCP as opposed to self-testing. Updated for consistency with Section 8.1.4.	nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial01·
1.3 Schedule of Activities CCI	CCI		Nonsubstantial
2.2 Background	Added infonnation on rebound in COVID-19.	To provide clinical relevance on the addition of the population with rebound to this study.	nonsubstantial
4.1 Overall Design 9.0 Statistical Considerations 9.5 Sample Size Detennination	Defined timing of analyses, described primaiy and follow-up analyses, and stated that the additional population with rebound will be analyzed separately from the main study population.	To clarify data analysis.	nonsubstantial
5.3.2 Other Restrictions	Included exception for participants who have an oncology disease.	To avoid excluding pa1ticipants who are immunocomproinised with an oncology disease who are often participating in oncology clinical trials from the study population. To incorporate changes from the 12 July 2022 PACL.	nonsubstantial
6.1.1 Administration	Updated timing of dose adininistration.	To align with dosing administration in other C467 protocols.	nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
6.3 Assignment to Study Intervention	Added stratification text for participants in the main study population who are considered immunocompromised solely based on corticosteroids or TNF blocker use.	Updated for consistency.	nonsubstantial
6.9 Prior and Concomitant Therapy	Described ritonavir is an inhibitor of CYP3A4 and provided guidance accordingly.	To provide clinical guidance for participants who take concomitant medications metabolized by CYP3A4.	nonsubstantial
8.1.1.1 Medical History	Added that risk factors for the participant developing severe COVID-19 illness will be recorded.	To clarify medical history.	nonsubstantial
8.1.1.3 Secondary Contacts	Added that secondary contacts may be used to determine if a participant is lost to follow-up or vital status check.	To clarify utility of collecting secondary contact information.	nonsubstantial
8.4.1 Time Period and Frequency for Collecting AE and SAE Information 8.4.1.1 Reporting SAEs to Pfizer Safety 8.4.5.1 Exposure During Pregnancy 8.4.5.2 Exposure During Breastfeeding	Updated CT SAE Report Form and the EDP Supplemental Form to PSSA and added minor edits for clarification.	To align with Pfizer's new platform for submission of SAEs to the Drug Safety Unit.	nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial01· Nonsubstantial
8.4.5.3 Occupational Exposure 8.4.10 Medication En-ors 10.3.3 Recording/Rep 011ing and Follow-Up of AEs and/or SAEsDuring the Active Collection Period 10.3.4 Repo1ting of SAEs			
CCI [redacted]	[redacted]	[redacted]	[redacted]
9.2 Analysis Sets	Clarified that analysis sets will be applied for the main study population and the population with rebound.	To clarify analysis sets defined in the protocol will be applied to both populations.	nonsubstantial
10.2 Appendix 2: Clinical Laborato1y Assessments	Separated *urea* and *creatinine.*	To clarify they are 2 separate laboratory assessments. To incorporate changes from the 12 July 2022 PACL.	nonsubstantial
10.4.2. Female Paitici ant	Separated the pai·agraphs for WOCBP and WONCBP.	For clai·ification	nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Reproductive Inclusion Criteria			
Section 10.9.4 Immunocompromised Criteria Details	Clarified length of time for corticosteroid use prior to study entry.	To clarify corticosteroid use requirements.	nonsubstantial
Throughout the protocol	General editorial changes.	To correct grammatical errors, to maintain consistency, and/or to increase clarity.	nonsubstantial

TABLE OF CONTENTS

LIST OF TABLES 18
1. PROTOCOL SUMMARY 19
1.1. Synopsis 19
1.2. Schema 26
1.3. Schedule of Activities 27
2. INTRODUCTION 36
2.1. Study Rationale 36
2.2. Background 36
2.2.1. Clinical Overview 38
2.3. Benefit/Risk Assessment 38
2.3.1. Risk Assessment 39
2.3.2. Benefit Assessment 41
2.3.3. Overall Benefit/Risk Conclusion 41
3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS 41
4. STUDY DESIGN 43
4.1. Overall Design 43
4.2. Scientific Rationale for Study Design 44
4.2.1. Diversity of Study Population 45
4.2.2. Choice of Contraception/Barrier Requirements 45
4.2.3. Collection of Retained Research Samples 45
4.2.4. Inclusion of Pediatric Participants 45
4.3. Justification for Dose 46
4.4. End of Study Definition 47
5. STUDY POPULATION 47
5.1. Inclusion Criteria 47
5.2. Exclusion Criteria 48
5.3. Lifestyle Considerations 49
5.3.1. Contraception 49
5.3.2. Other Restrictions 50
5.4. Screen Failures 50
6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 50

6.1. Study Intervention(s) Administered....50
6.1.1. Administration....53
6.2. Preparation, Handling, Storage, and Accountability....54
6.2.1. Preparation and Dispensing....55
6.3. Assignment to Study Intervention....55
6.4. Blinding....56
6.4.1. Blinding of Participants....56
6.4.2. Blinding of Site Personnel....56
6.4.3. Blinding of the Sponsor....56
6.4.4. Breaking the Blind....56
6.5. Study Intervention Compliance....57
6.6. Dose Modification....58
6.7. Continued Access to Study Intervention After the End of the Study....58
6.8. Treatment of Overdose....58
6.9. Prior and Concomitant Therapy....59
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL....60
7.1. Discontinuation of Study Intervention....60
7.2. Participant Discontinuation/Withdrawal From the Study....61
7.2.1. Withdrawal of Consent....62
7.3. Lost to Follow-Up....62
8. STUDY ASSESSMENTS AND PROCEDURES....62
8.1. Administrative and Baseline Procedures....62
8.1.1. Baseline Procedures....63
8.1.1.1. Medical History....63
8.1.1.2. Study Kit....63
8.1.1.3. Secondary Contacts....64
8.1.2. Home Health Visits....64
8.1.3. Mobile Visits....64
8.1.4. Telehealth Visits....65
8.2. Efficacy Assessments....66
8.2.1. Participant Diary....66

8.2.2. COVID-19-Related Hospitalizations and Medical Details 66
8.2.3. Oxygen Support Details 66
8.2.4. PRO Assessments 66
8.2.4.1. Global Impression Questions 66
8.2.4.2. SF-36 v2® Health Survey (Acute Form) 67
8.2.4.3. WPAI 67
8.2.4.4. EQ-5D-5L Scale 67
8.2.5. COVID-19 Signs and Symptoms 68
8.3. Safety Assessments 68
8.3.1. Targeted Physical Examinations 68
8.3.2. Vital Signs 68
8.3.2.1. Blood Pressure and Pulse Rate 69
8.3.2.2. Temperature and Respiratory Rate 69
8.3.2.3. Oxygen Saturation Level 69
8.3.2.4. At-Home Devices for Vital Signs 69
8.3.3. Point-of-Care Serum Creatinine Assessments 69
8.3.4. Clinical Safety Laboratory Assessments 69
8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment 70
8.3.5. Pregnancy Testing 70
8.3.5.1. At-Home Pregnancy Testing 70
8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting 70
8.4.1. Time Period and Frequency for Collecting AE and SAE Information 71
8.4.1.1. Reporting SAEs to Pfizer Safety 72
8.4.1.2. Recording Nonserious AEs and SAEs on the CRF 72
8.4.2. Method of Detecting AEs and SAEs 72
8.4.3. Follow-Up of AEs and SAEs 72
8.4.4. Regulatory Reporting Requirements for SAEs 73
8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 73
8.4.5.1. Exposure During Pregnancy 73
8.4.5.2. Exposure During Breastfeeding 75
8.4.5.3. Occupational Exposure 75

8.4.6. Cardiovascular and Death Events....75
8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs....76
8.4.8. Adverse Events of Special Interest....76
8.4.8.1. Lack of Efficacy....76
8.4.9. Medical Device Deficiencies....76
8.4.10. Medication Errors....76
8.5. Pharmacokinetics....77
8.6. Genetics....78
8.6.1. Specified Genetics....78
8.6.2. Retained Research Samples for Genetics....78
8.7. Biomarkers....79
CCI
8.7.6. Specified Metabolomic Research....80
8.7.7. Retained Research Samples for Biomarkers....80
8.8. Immunogenicity Assessments....81
8.9. Health Economics....81
9. STATISTICAL CONSIDERATIONS....81
9.1. Statistical Hypotheses....81
9.1.1. Estimands....81
9.1.1.1. Primary Estimand/Coprimary Estimands....81
9.1.1.2. Secondary Estimands....81
9.1.2. Multiplicity Adjustment....82
9.2. Analysis Sets....82
9.3. Statistical Analyses....82
9.3.1. General Considerations....82
9.3.2. Primary Endpoint(s)/Estimand(s) Analysis....83

9.3.2.1. Definition of Endpoint(s)....83
9.3.2.2. Main Analytical Approach....83
9.3.2.3. Supplementary Analysis/Analyses....83
9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis....83
9.3.4. Tertiary/Exploratory Endpoint(s) Analysis....84
9.3.5. Safety Analyses....84
9.3.6. Other Analyses....85
9.4. Interim Analyses....85
9.5. Sample Size Determination....85
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS....87
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations....87
10.1.1. Regulatory and Ethical Considerations....87
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP....87
10.1.2. Financial Disclosure....88
10.1.3. Informed Consent/Assent Process....88
10.1.3.1. Informed Consent Process....88
10.1.3.2. Informed Assent Process....89
10.1.4. Data Protection....90
10.1.5. Committees Structure....91
10.1.5.1. Data Monitoring Committee....91
10.1.6. Dissemination of Clinical Study Data....91
10.1.7. Data Quality Assurance....92
10.1.8. Source Documents....93
10.1.9. Study and Site Start and Closure....94
10.1.10. Publication Policy....95
10.1.11. Sponsor's Medically Qualified Individual....95
10.2. Appendix 2: Clinical Laboratory Tests....97
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting....99
10.3.1. Definition of AE....99
10.3.2. Definition of an SAE....100

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period 101
10.3.4. Reporting of SAEs 104
10.4. Appendix 4: Contraceptive and Barrier Guidance 106
10.4.1. Male Participant Reproductive Inclusion Criteria 106
10.4.2. Female Participant Reproductive Inclusion Criteria 106
10.4.3. Woman of Childbearing Potential 106
10.4.4. Contraception Methods 107
10.5. Appendix 5: Genetics 109
10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines 110
10.7. Appendix 7: Age-Specific Kidney Function Calculation Recommendations 112
10.7.1. Adults (18 Years and Above)—2021 CKD-EPI Equations 112
10.7.1.1. Adolescents (12 Years to <18 Years)—Cockcroft-Gault Formula 112
10.7.2. Adverse Event Grading for Kidney Safety Laboratory Abnormalities 112
10.8. Appendix 8: Prohibited Concomitant Medications That May Result in DDI 113
10.9. Appendix 9: Eligibility Criteria 125
10.9.1. Age and Sex 125
10.9.2. Confirmed SARS-CoV-2 Infection Details for the Main Study Population 125
10.9.3. Signs and Symptoms Attributable to COVID-19 125
10.9.4. Immunocompromised Criteria Details 125
10.9.5. Inclusion Criteria for Additional Population With COVID-19 Rebound 126
10.9.6. Oxygen Saturation Criterion Details 127
10.9.7. Prior/Concomitant Therapy 127
10.10. Appendix 10: Participant-Reported COVID-19-Related Signs and Symptoms 128
10.11. Appendix 11: Abbreviations 129
11. REFERENCES 133

LIST OF TABLES

Table 1. Study Schedule of Assessment....27
Table 2. Width of 95% CI for the Proportion of Participants with Sustained NP Swab SARS-CoV-2 RNA <LLOQ....86
Table 3. Protocol-Required Safety Laboratory Assessments....97
Table 4. Drugs That are Contraindicated With Nirmatrelvir/Ritonavir....113
Table 5. Established and Other Potentially Significant Drug Interactions....116

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

An Interventional Efficacy And Safety, Phase 2, Randomized, Double-Blind, 3-Arm Study To Investigate Nirmatrelvir/Ritonavir in Nonhospitalized Participants at Least 12 Years Of Age With Symptomatic COVID-19 Who Are Immunocompromised

Brief Title:

A Study to Learn About the Study Medicine Called Nirmatrelvir/Ritonavir in People at Least 12 Years of Age With COVID-19 Who Are Immunocompromised

Regulatory Agency Identification Number(s):

US IND Number:	153517
EudraCT/CTIS Number:	2022-001362-35
ClinicalTrials.gov ID:	NCT05438602
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4671034
Phase:	2

Rationale:

Patients with COVID-19 who are immunocompromised are at increased risk of progressing to severe illness due to prolonged infection, limited contribution by the immune system in clearing the infection, and increased potential for viral resistance. Emergence of variants that are resistant to available treatment also puts the wider population at risk. Patients who are immunocompromised may benefit from extended treatment durations. The purpose of the study is to evaluate the efficacy and safety of nirmatrelvir/ritonavir (5, 10, and 15-day dosing durations) for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age and weigh ≥40 kg who are immunocompromised (main study population).

In addition, this study will also evaluate the efficacy and safety of a second treatment course of nirmatrelvir/ritonavir (5-, 10-, or 15-days) in an additional population of nonhospitalized symptomatic participants who are immunocompromised with a rebound in COVID-19 within 14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir (population with rebound).

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To describe the effect of nirmatrelvir/ritonavir on viral RNA levels in NP swabs over time for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44.	• The proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 in nonhospitalized, symptomatic patients ≥12 years of age with COVID-19 who are immunocompromised. This will be estimated without regard to study treatment discontinuation and considering participants receiving non-study antiviral or monoclonal antibody therapy post-baseline for the treatment of COVID-19 as not achieving sustained NP swab SARS-CoV-2 RNA <LLOQ.
Secondary:	**Secondary:**	**Secondary:**
• To describe the effect of nirmatrelvir/ritonavir treatment duration on the rate of sustained virologic clearance in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Time to first NP swab SARS-CoV-2 RNA<LLOQ (<2.0 $\log_{10}$ copies/mL) for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline. • Time to sustained NP swab SARS-CoV-2 RNA <LLOQ (<2.0 $\log_{10}$ copies/mL) through Day 44 for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline.	• Not applicable.
• To describe the effect of nirmatrelvir/ritonavir on viral clearance for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Proportion of participants with SARS-CoV-2 RNA <LLOQ in plasma over time. • Proportion of participants with SARS-CoV-2 RNA level in NP swabs <2.0 $\log_{10}$ copies/mL at each study visit through Day 44. • Change from baseline in SARS-CoV-2 RNA level in NP swabs and in plasma over time. • Rebound in SARS-CoV-2 RNA level in NP swabs at follow up (ie, any study visit after end of treatment through Day 44) that is defined as a half (0.5) $\log_{10}$ copies/mL increase or greater in SARS-CoV-2 RNA level relative to end of treatment SARS-CoV-2 RNA level based on treatment regimen, with a follow-up viral RNA level ≥2.5 $\log_{10}$ copies/mL.	• Not applicable.
• To describe the safety and tolerability of nirmatrelvir/ritonavir	• Incidence of TEAEs.	• Not applicable.

Objectives	Endpoints	Estimands
for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Incidence of SAEs and AEs leading to discontinuations.	
• To describe the effect of nirmatrelvir/ritonavir on hospitalization and all-cause mortality in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Proportion of participants with COVID-19-related hospitalization >24 hours, or death from any cause through Day 28. • Proportion of participants with death (all cause) through Week 24.	• Not applicable.
• To describe COVID-19 related healthcare resource utilization in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised and treated with nirmatrelvir/ritonavir.	• Proportion of participants with COVID-19-related hospitalization of any duration. • Proportion of participants with COVID-19-related ICU admission of any duration. • Proportion of participants requiring invasive mechanical ventilation or ECMO. • Number of days in hospital and ICU stay in participants with COVID-19-related hospitalization. • Number of COVID-19-related medical visits through Day 44 and through Week 24.	• Not applicable.
• To evaluate nirmatrelvir/ritonavir for the duration and severity of signs and symptoms in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Duration of each targeted COVID-19 signs/symptoms. • Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 44.	• Not applicable.
• To determine the PK of nirmatrelvir/ritonavir in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Nirmatrelvir and ritonavir PK in plasma and whole blood (if feasible).	• Not applicable.

Overall Design:

This Phase 2, randomized, double-blind study will evaluate the efficacy and safety of nirmatrelvir/ritonavir (5-, 10-, and 15-day dosing durations) for the treatment of COVID-19 in approximately 150 nonhospitalized symptomatic participants aged at least 12 years and weigh ≥40 kg who are immunocompromised (main study population). In addition, this study will also evaluate the efficacy and safety of a second treatment course of nirmatrelvir/ritonavir (5-, 10-, or 15-days) in an additional population of nonhospitalized symptomatic participants who are immunocompromised with a rebound in COVID-19 within

14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir (population with rebound).

Participants in the additional population with rebound will be recruited during the enrollment phase for the main study population. Enrollment of the population with rebound will stop after the main study population is fully enrolled or after 50 participants in the population with rebound have been enrolled, whichever occurs sooner.

Participants will be screened on the same day as randomization or 1 calendar day before randomization. The total study duration is up to 24 weeks, including study intervention administration through Day 15 or Day 16, safety assessments through Day 44, efficacy assessments through Week 24, and long-term follow-up at Weeks 12 and 24.

An independent E-DMC will review unblinded data to ensure the safety of participants on an ongoing basis throughout the duration of the study.

Number of Participants:

Up to approximately 200 participants will be enrolled in this study.

The study will randomize approximately 150 participants in a 1:1:1 randomization ratio, resulting in approximately 50 participants in each treatment arm (main study population). Randomization of the main study population will be stratified by those who are considered immunocompromised solely based on corticosteroids or TNF blocker use (yes/no). Enrollment of participants in the main study population considered immunocompromised based solely on receiving corticosteroids or TNF blockers will be capped at approximately 25%.

In addition, the study will also randomize an additional population of up to 50 nonhospitalized symptomatic participants (in a 1:1:1 randomization ratio) who are immunocompromised with a rebound in COVID-19 within 14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir (population with rebound).

Randomization for the population with rebound will not be stratified by those who are considered immunocompromised solely based on corticosteroids or TNF blocker use. Enrollment of participants considered immunocompromised based solely on receiving corticosteroids or TNF blockers in the additional population with rebound will not be capped.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent/assent process and screening. A participant will be considered enrolled if the informed consent/assent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

1. Participants aged 12 years or older and weighing ≥40 kg at screening.
    - Refer to protocol for reproductive criteria for female participants.
2. Confirmed SARS-CoV-2 infection as determined by RT-PCR or other acceptable test method in any specimen collected.
3. ≥1 sign/symptom attributable to COVID-19 present on the day of randomization.
4. Immunocompromised.

In addition, the following inclusion criteria only apply to the additional population with rebound:

5. Presenting with documented, symptomatic, COVID-19 rebound within 14 days following completion of an initial 5-day treatment course with nirmatrelvir/ritonavir.

Exclusion Criteria

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

1. Current need for hospitalization or anticipated need for hospitalization within 24h after randomization in the clinical opinion of the site investigator.
2. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class C, or acute liver failure.
3. History of hypersensitivity or other contraindication to any of the components of the study interventions, as determined by the investigator.
4. Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention.
5. Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator.

6. Receiving dialysis or have known age-specific eGFR <30 mL/min/1.73 m^2 or eCrCl <30 mL/min at screening as measured by a serum creatinine point of care device.

7. Oxygen saturation of <92% on room air obtained at rest within 24h prior to randomization.

8. 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.

9. Current use of any prohibited concomitant medication(s).

10. Current or previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Authorized or products with conditional approval are not considered investigational.

11. Prior participation in this trial.

12. Females who are pregnant up to <14 weeks gestation. Pregnancy ≥14 weeks is not exclusionary.

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

Study Arms and Duration:

Eligible participants for this study will be randomly assigned (1:1:1) to receive nirmatrelvir plus ritonavir orally q12h as specified in the table below.

Study Intervention(s)				
Intervention Name	Nirmatrelvir	Placebo for nirmatrelvir	Ritonavir	Placebo for ritonavir
Arm Name (group of participants receiving a specific treatment or no treatment)	nirmatrelvir/ritonavir	placebo	nirmatrelvir/ritonavir	placebo
Unit Dose Strength(s)	150 mg	0 mg	100 mg	0 mg
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP

Study Arm(s)			
Arm Title	Nirmatrelvir/ ritonavir 5-day	Nirmatrelvir/ ritonavir 10-day	Nirmatrelvir/ritonavir 15-day
Arm Type	Experimental, placebo	Experimental, placebo	Experimental
Arm Description	Participants will receive nirmatrelvir/ ritonavir 300 mg/100 mg (or 150 mg/100 mg for participants with eGFR ≥30 to <60 mL/min/1.73 m^2 or eCrCl ≥30 to <60 mL/min) q12h from Day 1 through Day 5 followed by placebo for nirmatrelvir/placebo for ritonavir q12h for Day 6 through Day 15.	Participants will receive nirmatrelvir/ ritonavir 300 mg/100 mg (or 150 mg/100 mg for participants with eGFR ≥30 to <60 mL/min/1.73 m^2 or eCrCl ≥30 to <60 mL/min) q12h from Day 1 through Day 10 followed by placebo for nirmatrelvir/placebo for ritonavir q12h for Day 11 through Day 15.	Participants will receive nirmatrelvir/ ritonavir 300 mg/100 mg (or 150 mg/100 mg for participants with eGFR ≥30 to <60 mL/min/1.73 m^2 or eCrCl ≥30 to <60 mL/min) q12h from Day 1 through Day 15.

Statistical Methods:

No formal hypothesis testing will be performed for this study.

The primary estimand, reported separately for the main study population and the population with rebound, is the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 in nonhospitalized symptomatic patients ≥12 years of age with COVID-19 who are immunocompromised. This will be estimated without regard to study treatment discontinuation and considering participants receiving non-study antiviral or monoclonal antibody therapy post-baseline for the treatment of COVID-19 as not achieving sustained NP swab SARS-CoV-2 RNA <LLOQ.

The efficacy and safety data will be analyzed and summarized separately for the main study population and the additional population with rebound.

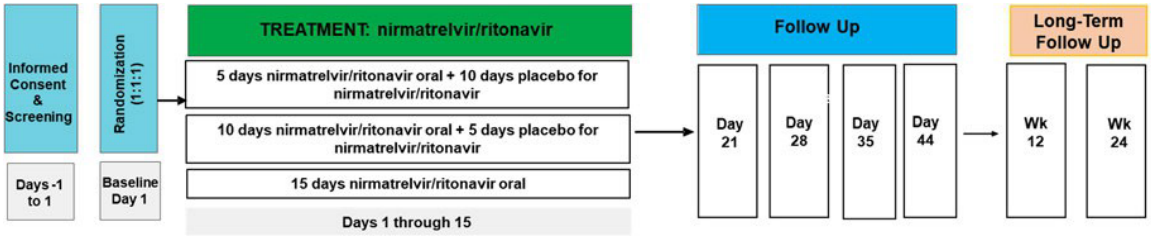
No formal interim analysis will be conducted for this study.

Ethical Considerations:

Previous studies have demonstrated efficacy, safety, and tolerability of nirmatrelvir/ritonavir in adults at increased risk of progressing to severe COVID-19 illness, which included participants who were immunocompromised. The FDA has granted EUA for nirmatrelvir/ritonavir for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Because people who are immunocompromised are less likely to mount a robust immune response if infected, they may benefit from an extended duration of nirmatrelvir/ritonavir. The most common adverse events described with nirmatrelvir/ritonavir treatment are allergic reactions, change in taste, diarrhea, headache, and vomiting. Taking into account the measures to minimize risk to study participants, the potential risks identified in association with nirmatrelvir/ritonavir are justified by the anticipated benefits that may be afforded to participants who are immunocompromised. Additional potential benefit to individual pregnant study participants treated with nirmatrelvir/ritonavir may include reduction in risks associated with severe COVID-19 to pregnancy and pregnancy outcome, such as serious morbidity from obstetric complications, preeclampsia, gestational diabetes, preterm birth, low birth weight, and stillbirth.

Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants must avoid use of a non-study antiviral or monoclonal antibody therapy for the treatment of COVID-19 within 15 days after randomization, except for participants who progress to severe or critical COVID-19. Female participants of childbearing potential must agree to use appropriate contraception methods.

1.2. Schema



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 infonnation 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 paiiicipant.

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be found in Se.ction 10.11.	Sc1·eening	Baseline (Day 1)	Day5	Day 10	Day 15	Day 21	Day 28	Day 35	Day 44	LTF/U		ET (pliol' • to Day. 44)	Notes
										Week 12	Week 24		
Visit Window	**Day-1 to Dayl**	**0 days**	**1 day**	1±1 da)	**±2 days**	**±2 days**	**±2 days**	±3 **days**	±3 **days**	±7 **days**	±7 **days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1, and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedures that are listed to occur at both visits only need to be completed once.
Study Visit Location	S	S	S	**S**	**SIP**	**SIP**	***SIP***	***SIP***	***SIP***	***SIP***	***SIP***	**SIP**	• All study visits are expected to be in-person visits. Site staff should, in discussion with participants, detennine the most appropriate location to conduct study visits. Visits should take place at the investigational site (S). If this is not feasible, then alternate venues may include the participant's location (P). Refer to Section 8.1.2 and Section 8.1.3. • If an in-person visit is held at a location other than the investigational site, the HCP perfonning the visit should perform all assessments. If the HCP is unable to collect all required information for the study visit (eg, AEs, concomitant medications, contraception), the site should contact the participant via a follow-up telephone call to collect the additional infonnation possible. Refer to Section 8.1.4.
ELIGIBILITY													
Infonued consent (and assent if applicable)	X												• Infonued consent/assent should be obtained prior to undergoing anv studv-soecific orocedm·es.

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be found in Se.ction 10.11.	Sc1·eening	Baseline (Day 1)	Day5	Day 10	Day 15	Day 21	Day 28	Day 35	Day 44	LTF/U		ET (pliol' • to Day. 44)	Notes
										Week 12	Week 24		• Day relative to start of study intervention (Day 1). Baseline (Day 1) visit is a mandatory site visit. • Assessments indicated in brackets fXl are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day-1 to Dayl**	**0 days**	lf:1 day	lf:1 da)	**±2 days**	**±2 days**	**±2 days**	±3 **days**	±3 **days**	***±1*** **days**	±7 **days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1, and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedures that are listed to occur at both visits only need to be completed once.
													• See Se-ction 10.1.3 for additional information.
Verify inclusion/exclusion criteria	X												• See Se-ction 5.1 and Section 5.2.
Demographics and medical historv	X												• See Se-ction 8.1.1.1.
Physical Examination and Vital Shms													
Targeted physical examination	**X**	**X**											• Physical examinations to be completed before administration of study intervention. • See Se-ction 8.3.1.
Vital signs	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**	• See Se-ction 8.3.2 and Section 8.1.4.
Weight, height	**X**												• Height may be self-repo,ted for paiticipants ::::18 years of age. • See Se-ction 8.3.1.
Vital status check										**X**	**X**	**X**	• Seconda,y contacts may be used for a vital status check.
Laboratory Assessments													• See Section 8.3.4 for additional **information.** • See Appendix 2 **for a** list of Clinical **Laboratory tests** to **be done.** • For laboratory **collection volumes, see the laboratory manual.**
Hematology		**X**	**X**	**X**	**X**	**[X]**	**[X]**	**[X]**	**[X]**			**[X]**	• Baseline laborato,y assessments should be collected prior to first dose of study intervention. • If deemed necessary to confirm eligibility, laborato,y assessments at screening may be pe1fo1med at the local laborato1y at the investigator's discretion.
Blood chemistry		**X**	**X**	**X**	**X**	**[X]**	**[X]**	**[X]**	**[X]**			**[X]**	

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be found in Se.ction 10.11.	Sc1·eening	Baseline (Day 1)	Day5	Day 10	Day 15	Day 21	Day 28	Day 35	Day 44	LTF/U		ET (pliol' • to Day. 44)	Notes
										Week 12	Week 24		Day relative to start of study intervention (Day 1). Baseline (Day **1)** visit is a mandatory site visit. • Assessments indicated in brackets fXl are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day-1 to Dayl**	**0 days**	lf:1 day	lf:1 da)	**±2 days**	**±2 days**	**±2 days**	±3 **days**	±3 **days**	*±1* **days**	±7 **days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1, and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedures that are listed to occur at both visits only need to be completed once.
Thyroid function		X		X	X				X			X	• Abnonual laborato1y values related to AEs should be followed until resolution.
SARS-CoV-2 Seroloev		X		X	X			X	X	X	X	X	
Point-of-care semm creatinine assessment	X	[X)	[X)	[X)									• Screening visit: A semm creatinine point-of-care device assessment for detenuining estimation of kidney function (eGFR for adults 18 years and older, and CrCl for adolescents 12 years to <18 years) is required for eligibility. See Section 10.7.1 for age specific kidney function calculations. • Baseline visit assessment expected only if screening and baseline visits are held on different days. • Day *5* and/or Day 10 assessment to be pe,formed at discretion of the investigator. • See Se.ction 8.3.3.
Pregnancy test	X								X			X	• A negative urine or semm beta human chorionic gonadotropin (P-hCG) pregnancy test must be confinued at screening for only WOCBP who are not pregnant at screening. Pregnancy tests will also be done whenever 1 menstmal cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at Day 44 or ET visit. • See Se.ction 8.3.5 and Section 8.1.4.
FSH	X												• FSH is to be pe,fonued to confinu postmenopausal status in female pa,ticipants <60 years of age at screening who are not using hormonal contraception or ho,monal replacement therapy. Female participants aged 50 to 60 vears with no menses for 12 months do

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be fonnd in Se.ction 10.11.	Sc1·eening	Baseline (Day 1)	Day 5	Day 10	Day 15	Day 21	Day 28	Day 35	Day 44	Week 12	Week 24	ET (pliol' to Day 44)	Notes Day relative to start of study intervention (Day 1). Baseline (Day **1)** visit is a mandatory site visit. Assessments indicated in brackets fXl are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day -1 to Dayl**	**0 days**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	Screening procedures may be done from Day -1 to Day 1, and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedures that are listed to occur at both visits on! need to be com leted once.
													not need FSH testing to be performed to confinn postmenopausal status. • When FSH testing is required to confinn postmenopausal status, a participant may be enrolled in the study prior to the test result being available as long as the FSH test result confinns postmenopausal status prior to dosing. A female whose menopausal status is in doubt will be required to use a highly effective method of contraception during the study (Section 10.4.4). • See Se-ction 10.4.2 and Section 10.2.
CCI													

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be fonnd in Se.ction 10.11.	Sc1·eening	Baseline (Day 1)	Day 5	Day 10	Day 15	Day 21	Day 28	Day 35	Day 44	Week 12	Week 24	ET (pliol' to Day 44)	Notes Day relative to start of study intervention (Day 1). Baseline (Day **1)** visit is a mandatory site visit. Assessments indicated in brackets fXl are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day -1 to Dayl**	**0 days**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±3 days**	*±1* **days**	±7 **days**	**±5 days**	Screening procedures may be done from Day -1 to Day 1, and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedures that are listed to
[redacted]													
PK Assessments													
PK sampling (ninuatrelvir and ritonavir)		X	X	X	X							[X]	• At baseline/Day 1, the time of sample collection is 1-2h after dose administration. • On Day 5, Day 10, and Day 15, one venous blood sample for PK will be collected on each day at any time dtuing the visit. PK sample will be collected at ET visit only if the ET visit occtu·s within 2 days (48h) of the last dose of study intervention. • See Se.ction 8.5.
tud Intervention													
Rando atio													S . Secfon 6.3.

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be found in Se.ction 10.11.	Sc1·eening	Baseline (Day 1)	Day5	Day 10	Day 15	Day 21	Day 28	Day 35	Day 44	LTF/U Week 12	LTF/U Week 24	ET (pliol'• to Day. 44)	Notes
Visit Window	**Day-1 to Dayl**	**0 days**	bl:1 day	bl:1 da)	**±2 days**	**±2 days**	**±2 days**	±3 **days**	±3 **days**	*±1* **days**	±7 **days**	**±5 days**	• Day relative to start of study intervention (Day 1). Baseline (Day **1)** visit is a mandatory site visit. • Assessments indicated in brackets fXl are only to be conducted if indicated as described in the "Notes". • Screening procedures may be done from Day -1 to Day 1, and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedures that are listed to occur at both visits onlv need to be completed once.
Study intervention dispensation		**X**	**X**	**X**									• Study intervention will be dispensed on Day 1, Day *5,* and Day 10 (see Section 6.1.1). • Should eGFR or eCrCl (based on the point-of-care creatinine) on Day *5* or Day 10 wan-ant a dose modification, replacement study intervention will be dispensed on Day *5* or Day 10. See Se-ction 10.7.1 for age specific kidney function calculations. • See Se-ction 6.6.
Study intervention administration		Day 1 through Day 15											• Baseline assessments should be pe1fo1med before administration of the first study intervention, except for **PK** sampling. • The first dose of study intervention will be administered to all pa1ticipants on Day 1 during the in person visit. All subsequent doses of study intervention (ie, 29) will be self-administered (or administered to the pa1ticipant by a legal guardian or caregiver). If only 1 dose of study intervention is administered on Day 1, study intervention administration should end on Day 16. • See Se-ction 6.1.1.
Study Intel'Vention Accountability													
Retrieval of unused study intervention and empty study intervention containers			**X**	**X**	**X**							**X**	• If the Day 15 visit is conducted prior to last dose of study intervention, empty study intervention containers and unused study intervention should be retumed at the Day 21 visit. • See Se-ction 6.5.

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be found in Se.ction 10.11.	Sc1·eening	Baseline (Day 1)	Day5	Day 10	Day 15	Day 21	Day 28	Day 35	Day 44	LTF/U Week 12	LTF/U Week 24	ET (pliol'• to Day. 44)	Notes Day relative to start of study intervention (Day 1). Baseline (Day **1**) visit is a mandatory site visit. • Assessments indicated in brackets fXl are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day-1 to Dayl**	**0 days**	bl:1 day	bl:1 da)	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±3 days**	*±1* **days**	±7 **days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1, and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedures that are listed to occur at both visits onlv need to be completed once.
Study intervention accountability			**X**	**X**	**X**							**X** [if !needed 1	• Study intervention accountabilityis only pe1fo1med at the Day 21 visit if the participant administered treatment after the Day 15 visit was conducted.
Patient Repo11ed Outcomes													6nly adult participants (c::18 years of age) will be asked to omplete PRO assessments. • See Section 8.2.4.
Collection of global impression questions		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	• Participants will answer 3 global impression questions. • See Se.ction 8.2.4.1.
SF-36		**X**		**X**		**X**			**X**	**X**	**X**		• See Se.ction 8.2.4.2.
WPAI			**X**		**X**					**X**	**X**		• See Se-ction 8.2.4.3.
EQ-5D-5L		**X**	**X**		**X**				**X**	**X**	**X**		• See Se-ction 8.2.4.4.
lstudy Pl'ocedul'es & IA sessments													
Provide participants with studv emere:encv contact card	**X**												• See Section 10**.1.11.**
Collect/update seconda,y contacts		**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**			• See Se-ction 8.1.1.3.
Record oxygen suppo,t details	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**	• See Se-ction 8.2.3.
Study kit dispensed and participant instmcted on its use		**X**											• See Se-ction 8.1.1.2.
Pa,ticipant-completed study intervention log		Daily on Day **1** through Day 15											• Study intervention logshould be completed daily on Days 1 through Day 16 if only 1 dose was administered on Day 1. • See Se-ction 8.2.1.

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be found in Se.ction 10.11.	Sc1·eening	Baseline (Day 1)	Day5	Day 10	Day 15	Day 21	Day 28	Day 35	Day 44	LTF/U Week 12	LTF/U Week 24	ET (pliol'• to Day. 44)	Notes
													Day relative to start of study intervention (Day 1). Baseline (Day **1)** visit is a mandatory site visit. • Assessments indicated in brackets fXl are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day-1 to Dayl**	**0 days**	bl:1 day	bl:1 da)	**±2 days**	**±2 days**	**±2 days**	±3 **days**	±3 **days**	*±1* **days**	±7 **days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1, and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedures that are listed to occur at both visits onlv need to be completed once.
Staff review of study intervention loQ,		Daily on Day 1 through Day 15											• See Se·ction 6.5.
Record COVID-19-related medical visits			X	X	X	X	X	X	X	X	X	X	• COVID-19-related medical visits a participant has attended since the last assessment will be collected. • See Se·ction 8.2.2.
Contraception check	X	X	X	X	X	X	X	X	X			X	• See Section 5.3.1, Section 8.1.4, and Annendix 4.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X			X	• All prescription and over-the-counter medications including vaccines taken by the pa1ticipant within 30 days before study entty (considered prior tt-eattuent) will be recorded. • COVID 19-related vaccinations and monoclonal antibody or antiviral treattuent for the tt-eattuent of COVID-19 at any time prior to the planned first dose will also be collected. • Concomitant therapies will be collected thrnugh the Day 44 visit or at ET visit. • See Se·ction 6.9 and Section 8.1.4.
Adjunctive therapeutic procedm·es	X	X	X	X	X	X	X	X	X			X	• Will be collected through the Day 44 visit or at ET visit.
COVID-19 signs and svmotoms		X	X	X	X	X	X	X	X	X	X	X	• See Se·ction 8.2.5 and Appendix 10.
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X			X	• AEs should be assessed by means of a telehealth visit if not feasible via an in-person visit. • See Se·ction 8.1.4. • Previously identified AEs (either by interview, physical exam, or other assessment) should be monitored to the extent oossible if telehealth is used.

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be found in Se.ction 10.11.	Sc1·eening	Baseline (Day 1)	Day5	Day 10	Day 15	Day 21	Day 28	Day 35	Day 44	LTF/U		ET (pliol'• to Day. 44)	Notes
										Week 12	Week 24		Day relative to start of study intervention (Day 1). Baseline (Day **1)** visit is a mandatory site visit. • Assessments indicated in brackets fXl are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day-1 to Dayl**	**0 days**	bl:1 day	bl:1 da)	**±2 days**	**±2 days**	**±2 days**	±3 **days**	±3 **days**	*±1* **days**	±7 **days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1, and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedures that are listed to occur at both visits onlv need to be completed once.
													• After the defined active collection period for safety events, long-tenu follow-up visits are also conducted at Weeks 12 and 24. Any new SAE occtming dllling this long-term follow-up period and detenuined to be related to study intervention must be repo1ted to Pfizer Safety immediately upon awareness and under no cu·cU111Stance should this exceed 24 holll·s. • See Se-ction 8.4.3 for follow-up AE and SAE assessments.

2. INTRODUCTION

Nirmatrelvir, a potent and selective SARS-CoV-2 3CL orally administered protease inhibitor, is being investigated in participants with COVID-19 who are immunocompromised.

2.1. Study Rationale

Patients with COVID-19 who are immunocompromised are at increased risk of progressing to severe illness due to prolonged infection, limited contribution by the immune system in clearing the infection, and increased potential for viral resistance.[1,2] A limited number of participants who were immunocompromised participated in Study C4671005 (EPIC-HR, NCT04960202). Such patients may benefit from extended treatment durations. The purpose of the study is to evaluate the efficacy and safety of nirmatrelvir/ritonavir (5-day, 10-day, and 15-day dosing durations) for the treatment of COVID-19 in nonhospitalized, symptomatic participants ≥12 years of age and weighing at least 40 kg who are immunocompromised (main study population).

In addition, this study will also evaluate the efficacy and safety of a second treatment course of nirmatrelvir/ritonavir (5-, 10-, or 15-days) in an additional population of nonhospitalized symptomatic participants who are immunocompromised with a rebound in COVID-19 within 14 days following completion of an initial 5--day treatment course of nirmatrelvir/ritonavir (population with rebound).

2.2. Background

COVID-19, caused by the SARS-CoV-2 coronavirus, was declared a global pandemic by the WHO on 11 March 2020,[3] and continues to be a serious global threat to public health and to health care systems. As of 07 March 2022, COVID-19 has infected at least 446 million people, and has led to at least 6 million deaths worldwide.[4]

In order to prevent SARS-CoV-2 infection, several COVID-19 vaccines have been approved or authorized for emergency use by Health Authorities and are being administered globally.[5] Duration and sufficiency of vaccine protection may be inadequate in patients who are immunocompromised.[2,6] Even with the administration of a booster dose, immunocompromised patients may be less likely to develop strong immune protection from vaccines.

Currently authorized/approved vaccines may not be as effective against potential outbreaks from new coronavirus variants.[7] Emergence of the omicron variant in late 2021 provides an example of the potential impact emerging variants of SARS-CoV-2 may have on vaccine efficacy. More specifically, gene mutations in the omicron variant appear to result in vaccine efficacy against symptomatic disease that is significantly lower than against the Delta variant.[7] The omicron variants account for almost all SARS-CoV-2 infections in the US as of mid-January 2022.[8]

A limited number of antiviral agents and monoclonal antibody-based regimens have been approved or have received EUA by the FDA for the treatment of nonhospitalized high-risk patients with symptomatic COVID-19.[9] In December 2021, four anti-SARS-CoV-2

monoclonal antibody products have received EUA for the treatment of nonhospitalized patients with mild-to-moderate COVID-19. However, distribution of these agents have been paused as Omicron variants of concern (BA.1 and BA.2) have reduced in vitro susceptibility to these agents and these antibody regimens are not expected to provide clinical benefit.[9]

An additional preventive treatment, tixagevimab co-packaged with cilgavimab, has received EUA for pre-exposure prophylaxis in patients with moderate to severe immune compromise.[10]

In December 2021, the FDA granted EUA for a 5 day course of treatment for 2 separate oral antiviral agents, nirmatrelvir/ritonavir[11] and molnupiravir[12], for the treatment of COVID-19 in adult and pediatric patients 12 years of age and older who weigh at least 40 kg, with mild to moderate COVID-19 who are at high risk for progressing to severe illness. Molnupiravir is not recommended during pregnancy, as findings from animal reproduction studies showed that molnupiravir may cause fetal harm when administered to pregnant individuals. In January 2022, remdesivir received approval for this same population.[13] This treatment is administered by IV infusion over 3 days for nonhospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe illness.

Case reports in the literature describe individuals in the general population who have experienced symptomatic relapses of SARS-CoV-2 infection following completion of a 5-day course of nirmatrelvir/ritonavir.[14-16] The time course of symptom rebound suggests that symptom recurrence is likely not related to re-exposure and that it does not reflect a potential re-infection event. A retrospective review of 483 high-risk patients treated with nirmatrelvir/ritonavir reported 4 (0.8%) of patients experienced rebound of symptoms. Median time to rebound was reported as 9 days.[17] Rapid recurrence in symptoms along with a positive RT-PCR or rapid antigen test following the completion of a 5-day course of nirmatrelvir/ritonavir may indicate these patients require additional therapy to achieve sustained viral clearance.

Certain comorbidities and characteristics such as an immunocompromised status and older age increase an individual's risk for developing severe COVID-19.[18,19] COVID-19 may pose a unique threat to patients who are immunocompromised because COVID-19 vaccines are less effective in preventing infection.[2,6] In addition, immunocompromised patients may be at risk for prolonged infection. Prolonged viral shedding in immunocompromised patients with influenza infection is well-documented and is associated with an increased frequency of treatment-resistant virus variants.[20,21] Prolonged viral shedding in immunocompromised patients with SARS-CoV-2 infection has also been observed and has been associated with the emergence of treatment-resistant and novel virus variants.[22,23]

Given the risk for prolonged viral infection in patients who are immunocompromised, this patient population may benefit from longer duration therapy.

In this study of participants with symptomatic COVID-19 who are immunocompromised (including an additional population of symptomatic participants with rebound in COVID-19), nirmatrelvir/ritonavir will be administered for 5, 10, or 15 days.

2.2.1. Clinical Overview

The safety and efficacy of a 5-day treatment with nirmatrelvir/ritonavir in adults was demonstrated in Study C4671005 (EPIC-HR, NCT094960202), which enrolled nonhospitalized symptomatic adults, including participants who were immunocompromised, with laboratory-confirmed diagnosis of SARS-CoV-2 infection with at least 1 risk factor for progression to severe disease and with a COVID-19 symptom onset of ≤5 days. In the analysis of the primary endpoint from all participants enrolled in Study C4671005, an 89% reduction in COVID-19-related hospitalization or death from any cause compared with placebo in participants treated within 3 days of symptom onset was observed. 0.72% of participants who received nirmatrelvir/ritonavir were hospitalized through Day 28 following randomization (5 of 697 hospitalized with no deaths), compared to 6.45% of participants who received placebo and were hospitalized or died (44 of 682 hospitalized with 9 subsequent deaths) ($p<0.001$). In a secondary endpoint, nirmatrelvir/ritonavir reduced the risk of hospitalization or death for any cause by 88% compared with placebo in participants treated within 5 days of symptom onset; 0.77% of patients who received nirmatrelvir/ritonavir were hospitalized through Day 28 following randomization (8 of 1039 hospitalized with no deaths) compared with 6.31% of patients who received placebo (66 of 1046 hospitalized with 12 subsequent deaths) ($p<0.001$). Treatment with nirmatrelvir/ritonavir was safe and well tolerated.[24]

On 22 December 2021, the US FDA granted EUA to nirmatrelvir/ritonavir for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing ≥40 kg) who are at risk for progression to severe disease.[11]

Refer to the IB[25] for more details on studies, including clinical efficacy, safety, and PK results for completed and ongoing studies.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of nirmatrelvir/ritonavir 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(s): Nirmatrelvir		
Emesis	In Study C4671005, vomiting occurred at a greater frequency in the nirmatrelvir/ritonavir group than in the placebo group.	AEs will be monitored, and participants may receive antiemetics if needed.
Hypertension	Transient increases in systolic, diastolic, and mean blood pressure were observed in the preclinical studies. In Study C4671005 (adults at high risk for severe disease), a small imbalance in hypertension AEs (1% vs <1%) was reported.	Vital signs and all AEs will be monitored in the study. Refer to Section 8.4.
Reduced maternal and fetal weight	In rabbit embryo-fetal development toxicity studies, nirmatrelvir-related lower maternal body weight change and food consumption were observed at 1000 mg/kg/day but were not considered adverse based on low magnitude of difference from control and lack of impact on absolute body weights. Nirmatrelvir -related, adverse, lower fetal weight (0.91x control) was observed at 1000 mg/kg/day.	Lower dose of 300 mg q12h is used in this study.
Study Intervention(s): Ritonavir		
Gastrointestinal disturbances (including diarrhea, nausea, vomiting and abdominal pain)	Frequently reported adverse reaction in HIV-positive patients who are HIV-positive at 600 mg BID.	Lower dose of 100 mg twice daily is used in this study. There will be close observation of AEs. In addition to ongoing review of AEs by the sponsor, an E-DMC will review safety data as described in Section 10.1.5.1. Taking study intervention with food may improve tolerability.
Neurological disturbances (eg, paresthesia, including oral paresthesia, dysgeusia and dizziness)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		In addition to ongoing review of AEs by the sponsor, an E-DMC will review safety data as described in Section 10.1.5.1.
Rash (most commonly reported as erythematous and maculopapular, followed by pruritic)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs and monitoring through targeted physical exams. If needed therapeutic interventions per SoC may be provided.
Fatigue/Asthenia	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs.

2.3.2. Benefit Assessment

Nirmatrelvir/ritonavir has been shown to have SARS-CoV-2 antiviral activity in vitro. Efficacy, safety, and tolerability of nirmatrelvir/ritonavir was demonstrated in adults at increased risk of progressing to severe COVID-19 illness, which includes participants who are immunocompromised. The EMA has granted conditional approval for nirmatrelvir/ritonavir for the treatment COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.[26] The FDA has granted EUA for nirmatrelvir/ritonavir[11] for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older and weighing ≥40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Because people who are immunocompromised are less likely to mount a robust immune response if infected, potential benefits from an extended duration of nirmatrelvir/ritonavir therapy may include a shorter time to reduction in viral RNA levels, clinical recovery, prevention of hospitalization, and a lower probability of progressing to more severe illness or death.

2.3.3. Overall Benefit/Risk Conclusion

Considering the current COVID-19 global pandemic, the high burden of both mortality and morbidity, the potential for future epidemic outbreaks, the lack of readily available outpatient treatment options, and the measures taken to minimize risk to study participants, the potential risks identified in association with nirmatrelvir/ritonavir are justified by the anticipated benefits that may be afforded to participants who are immunocompromised.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To describe the effect of nirmatrelvir/ritonavir on viral RNA levels in NP swabs over time for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44.	• The proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 in nonhospitalized, symptomatic patients ≥12 years of age with COVID-19 who are immunocompromised. This will be estimated without regard to study treatment discontinuation and considering participants receiving non-study antiviral or monoclonal antibody therapy post-baseline for the treatment of COVID-19 as not achieving sustained NP swab SARS-CoV-2 RNA <LLOQ.
Secondary:	**Secondary:**	**Secondary:**
• To describe the effect of nirmatrelvir/ritonavir treatment duration on the rate of sustained virologic clearance in	• Time to first NP swab SARS-CoV-2 RNA<LLOQ (<2.0 $\log_{10}$ copies/mL) for participants with NP swab	• Not applicable.

Objectives	Endpoints	Estimands
nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	SARS-CoV-2 RNA ≥LLOQ at baseline. • Time to sustained NP swab SARS-CoV-2 RNA <LLOQ (<2.0 log_{10} copies/mL) through Day 44 for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline.	
• To describe the effect of nirmatrelvir/ritonavir on viral clearance for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Proportion of participants with SARS-CoV-2 RNA <LLOQ in plasma over time. • Proportion of participants with SARS-CoV-2 RNA level in NP swabs <2.0 log_{10} copies/mL at each study visit through Day 44. • Change from baseline in SARS-CoV-2 RNA level in NP swabs and in plasma over time. • Rebound in SARS-CoV-2 RNA level in NP swabs at follow up (ie, any study visit after end of treatment through Day 44) that is defined as a half (0.5) log_{10} copies/mL increase or greater in SARS-CoV-2 RNA level relative to end of treatment SARS-CoV-2 RNA level based on treatment regimen, with a follow-up viral RNA level ≥2.5 log_{10} copies/mL.	• Not applicable.
• To describe the safety and tolerability of nirmatrelvir/ritonavir for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	• Not applicable.
• To describe the effect of nirmatrelvir/ritonavir on hospitalization and all-cause mortality in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Proportion of participants with COVID-19-related hospitalization >24 hours, or death from any cause through Day 28. • Proportion of participants with death (all cause) through Week 24.	• Not applicable.
• To describe COVID-19 related healthcare resource utilization in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised and treated with nirmatrelvir/ritonavir.	• Proportion of participants with COVID-19-related hospitalization of any duration. • Proportion of participants with COVID-19-related ICU admission of any duration. • Proportion of participants requiring invasive mechanical ventilation or ECMO. • Number of days in hospital and ICU stay in participants with COVID-19-related hospitalization.	• Not applicable.

Objectives	Endpoints	Estimands
	• Number of COVID-19-related medical visits through Day 44 and through Week 24.	
• To evaluate nirmatrelvir/ritonavir for the duration and severity of signs and symptoms in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Duration of each targeted COVID-19 signs/symptoms. • Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 44.	• Not applicable.
• To determine the PK of nirmatrelvir/ritonavir in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Nirmatrelvir and ritonavir PK in plasma and whole blood (if feasible).	• Not applicable.

4. STUDY DESIGN

4.1. Overall Design

This Phase 2, randomized, double-blind, study will evaluate the efficacy and safety of nirmatrelvir/ritonavir (5-, 10-, and 15-day dosing durations) for the treatment of COVID-19 in approximately 150 nonhospitalized symptomatic participants aged at least 12 years and weigh ≥40 kg who are immunocompromised (main study population). In addition, this study will also evaluate the efficacy and safety of a second treatment course of nirmatrelvir/ritonavir (5-, 10-, or 15-days) in an additional population of nonhospitalized symptomatic participants who are immunocompromised with a rebound in COVID-19 within 14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir (population with rebound).

Participants in the additional population with rebound will be recruited during the enrollment phase for the main study population. Enrollment of the population with rebound will stop after the main study population is fully enrolled or after 50 participants in the population with rebound have been enrolled, whichever occurs sooner.

Eligible participants (main study population and additional population with rebound) for this study will be randomly assigned (1:1:1) to receive:

- nirmatrelvir plus ritonavir orally q12h for 5 days followed by placebo for nirmatrelvir plus ritonavir q12h for 10 days; or
- nirmatrelvir plus ritonavir orally q12h for 10 days followed by placebo for nirmatrelvir plus ritonavir q12h for 5 days; or
- nirmatrelvir plus ritonavir orally q12h for 15 days.

Participants will be screened on the same day as randomization or 1 calendar day before randomization. For the main study population, enrollment of participants considered immunocompromised based solely on receiving corticosteroids or TNF blockers will be capped at approximately 25%. Enrollment of participants considered immunocompromised based solely on receiving corticosteroids or TNF blockers in the additional population with rebound will not be capped.

For the main study population, randomization will be stratified by those who are considered immunocompromised solely based on corticosteroids or TNF blocker use (yes/no) (Section 10.9.4, Point #4). Randomization for the population with rebound will not be stratified by those who are considered immunocompromised solely based on corticosteroids or TNF blocker use.

The total study duration is up to 24 weeks, including study intervention administration through Day 15 or Day 16, safety assessments through Day 44, efficacy assessments through Week 24, and long-term follow-up at Weeks 12 and 24.

Analyses will be conducted after the main study population is fully enrolled and have completed the Day 44 visit regardless of the number of randomized participants in the population with rebound. There will be 2 analysis time points for reporting the results of this study. The primary analysis will be performed after all participants in the main study population have completed the Day 44 visit. The follow-up analysis will be performed after all participants in the main study population have completed the Week 24 visit. In addition, both analyses (primary and follow-up) will include separate results for the main study population and the additional population with rebound.

An independent E-DMC will review unblinded data to ensure the safety of participants on an ongoing basis throughout the duration of the study (Section 10.1.5.1).

4.2. Scientific Rationale for Study Design

Patients with COVID-19 who are immunocompromised are at increased risk of progressing to severe illness due to prolonged infection, limited contribution by the immune system in clearing the infection, and increased potential for viral resistance.[1,2] Emergence of variants that are resistant to available treatment also puts the wider population at risk. Patients who are immunocompromised may benefit from extended treatment durations. The purpose of the study is to evaluate the efficacy and safety of nirmatrelvir/ritonavir (5, 10, and 15-day dosing durations) for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age and weigh ≥40 kg who are immunocompromised (main study population).

In addition, this study will also evaluate the efficacy and safety of a second treatment course of nirmatrelvir/ritonavir (5-, 10-, or 15-days) in an additional population of nonhospitalized symptomatic participants who are immunocompromised with a rebound in COVID-19 within 14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir (population with rebound).

4.2.1. Diversity of Study Population

This is a global study and the US diversity strategy will include sites with the potential to support the recruitment of diverse populations. In the US, medical institutions with varying characteristics, such as urban and suburban institutions, will be included. The strategy to help ensure diversity includes:

- Providing investigators with recruitment materials for both potential participants and other HCPs;
- Creating individual site recruitment plans in collaboration with sites and providing supplemental diverse recruitment tools;
- Developing recruitment and retention materials using imagery along with culturally and linguistically appropriate language to resonate with underrepresented populations;
- Translating all patient-facing materials into US Spanish;
- Educating site staff on the importance of including diverse participants;
- Monitoring diverse enrollment, in real time;
- Implementing additional strategies to mitigate trending below goals.

4.2.2. Choice of Contraception/Barrier Requirements

Human reproductive safety data are limited for nirmatrelvir/ritonavir, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required for female participants who are not pregnant at entry (see Appendix 4).

4.2.3. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.2.4. Inclusion of Pediatric Participants

Individuals of all ages are susceptible to SARS-CoV-2 infection. While younger patients appear to be less affected than the adult population and typically present with milder symptoms, children are at risk for MIS-C. Certain subsets of the pediatric population may present with severe disease, requiring hospitalization and intensive care. Risk factors for severe disease include neonatal age group and pre-existing medical conditions including children who are immunocompromised. There is an urgent need for safe and effective therapeutic interventions for individuals of all age groups that can reduce viral transmission, improve time to clinical recovery and prevent the progression of infection to more severe disease, hospitalization, and death in the current COVID-19 epidemic, as well as for potential future coronavirus epidemics.

This study includes participants of 12 years of age and older and weighing ≥40 kg, which is consistent with the Fact Sheet for nirmatrelvir/ritonavir where FDA has granted EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older and weighing ≥40 kg).[11]

4.3. Justification for Dose

On 22 December 2021, the US FDA granted EUA to nirmatrelvir/ritonavir for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kg) who are at risk for progression to severe disease, including patients who are immunocompromised. The recommended dose is 300 mg nirmatrelvir co-administered with 100 mg ritonavir q12h for 5 days. This dose was well tolerated in EPIC-HR and reduced the rate of hospitalization or death by 89% compared with placebo in symptomatic adult participants with COVID-19 who were at increased risk of progression to severe disease.

Based on pharmacokinetic modelling and simulation, the authorized dosing regimen is expected to result in comparable plasma exposures of nirmatrelvir and ritonavir in participants 12 years of age and older and weighing ≥40 kg as observed in adults.

In this study, in addition to the authorized 5-day treatment regimen of nirmatrelvir/ritonavir (300/100 mg q12h), 10-day and 15-day treatment durations will be studied. Patients who are immunocompromised may have higher viral RNA levels and prolonged viral shedding, which has been associated with more severe COVID-19 and the development of resistant viral variants. Consequently, these patients may benefit from longer anti-viral treatment durations to prevent an increase in viral RNA levels once treatment is completed. A quantitative systems pharmacology model of SARS-CoV-2 infection has been developed to describe SARS-CoV-2 viral RNA dynamics and was used to simulate the effects of different nirmatrelvir/ritonavir treatment durations in immunocompromised patients.[27] In order to assess the ability of longer treatment durations to mitigate the risk of viral rebound, this model was used to predict that a nirmatrelvir/ritonavir dosing duration of 10 days will result in a viral RNA reduction similar to the viral RNA reduction that is observed in the nonimmunocompromised patients treated for 5 days. An additional reduction in viral RNA is predicted with a 15-day treatment regimen.

Results from a first-in-human study in healthy participants showed a clinically acceptable safety profile up to the highest dose and exposure evaluated (500 mg of nirmatrelvir plus 100 mg of ritonavir twice daily for 10 days).[28] The safety and effectiveness of nirmatrelvir/ritonavir have not been established in pediatrics.

Results from the renal impairment study showed that the adjusted geometric mean (90% CI) test/reference ratios comparing moderate renal impairment (test) to normal renal function (reference) for nirmatrelvir AUC_{inf} and C_{max} was 187.40% (148.52%, 236.46) and 138.12% (113.18%, 168.55%), respectively.[29] Due to the increase in exposures of nirmatrelvir in those with moderate renal impairment, and verified by modeling and simulation, the nirmatrelvir/ritonavir dose in patients with moderate renal impairment was reduced to 150 mg/100 mg.

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit, or as shown in the SoA.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants aged 12 years or older and weighing ≥40 kg at screening (Appendix 9, Section 10.9.1).

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

Disease Characteristics:

2. Confirmed SARS-CoV-2 infection as determined by RT-PCR or other acceptable test method in any specimen collected as specified in Appendix 9, Section 10.9.2 for the main study population or Appendix 9, Section 10.9.5 for the additional population with rebound.

3. ≥1 sign/symptom attributable to COVID-19 present on the day of randomization (Appendix 9, Section 10.9.3).

4. Immunocompromised (Appendix 9, Section 10.9.4).

In addition, the following inclusion criteria only apply to the additional population with rebound:

5. Presenting with documented, symptomatic COVID-19 rebound within 14 days following completion of an initial 5-day treatment course with nirmatrelvir/ritonavir as specified in Appendix 9, Section 10.9.5.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Current need for hospitalization or anticipated need for hospitalization within 24h after randomization in the clinical opinion of the site investigator.

2. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class C, or acute liver failure.

3. History of hypersensitivity or other contraindication to any of the components of the study interventions, as determined by the investigator.

4. Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention.

5. Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator.

6. Receiving dialysis or have known age-specific eGFR <30 mL/min/1.73 m^2 or eCrCl <30 mL/min at screening as measured by a serum creatinine point of care device (Appendix 7, Section 10.7).

7. Oxygen saturation of <92% on room air obtained at rest within 24h prior to randomization. (See Appendix 9, Section 10.9.6).

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

Prior/Concomitant Therapy:

9. Current use of any prohibited concomitant medication(s) (see Section 6.9, Section 10.9.7, and Appendix 8).

Prior/Concurrent Clinical Study Experience:

10. Current or previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Authorized or products with conditional approval are not considered investigational.

11. Prior participation in this trial.

Other Exclusion Criteria:

12. Females who are pregnant up to <14 weeks gestation. Pregnancy ≥14 weeks is not exclusionary.

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

5.3. Lifestyle Considerations

5.3.1. Contraception

All female participants who are not pregnant at study entry, and who in the opinion of the investigator, are biologically capable of having children must agree to use a highly effective method of contraception consistently and correctly for at least 28 days after the last study intervention.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal female participant experiences menarche) or the risk of pregnancy changes (eg, a female participant who was not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.

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

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an

alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Other Restrictions

Participants may not participate in another interventional clinical study with an investigational compound, including those for COVID-19 therapeutics, through the long-term follow-up period. Participants who are in long-term follow-up in oncology or malignant hematology trials but who have not received investigational product within the timeline specified (see Section 5.2, Exclusion Criterion #10 for timeline) are eligible for enrollment provided they meet the other eligibility criteria defined in Section 5.

5.4. Screen Failures

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

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to nirmatrelvir 150 mg tablets and matching placebo and ritonavir 100 mg capsules and matching placebo.

6.1. Study Intervention(s) Administered

Study intervention will be self-administered by the participant OR administered to the participant by a legal guardian or caregiver.

A legal guardian or caregiver may administer study medication. Study personnel should review dose administration requirements with the participant, as appropriate, and with the delegated caregiver(s) (may include school nurse) before administration and throughout the study as necessary.

Study Intervention(s)				
Intervention Name	Nirmatrelvir	Placebo for nirmatrelvir	Ritonavir	Placebo for ritonavir
Arm Name (group of participants receiving a specific treatment or no treatment)	nirmatrelvir/ritonavir	placebo	nirmatrelvir/ritonavir	placebo
Type	drug	placebo	drug	placebo
Dose Formulation	tablet	tablet	capsule	capsule
Unit Dose Strength(s)	150 mg	0 mg	100 mg	0 mg
Dosage Level(s)	300 mg q12h for 5 days, 10 days, or 15 days 150 mg q12h for 5 days, 10 days, or 15 days (for participants with eGFR ≥30 to <60 mL/min/1.73 m^2 or eCrCl ≥30 to <60 mL/min at screening)	0 mg q12h for 5 days or 10 days	100 mg q12h for 5 days, 10 days, or 15 days	0 mg q12h for 5 days or 10 days
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IPM.	Provided centrally by the sponsor. Refer to the IPM.	Provided centrally by the sponsor. Refer to the IPM.	Provided centrally by the sponsor. Refer to the IPM.
Packaging and Labeling	Study intervention will be provided in blister wallets. Each	Study intervention will be provided in	Study intervention will be provided in HDPE bottles. Each	Study intervention will be provided in HDPE bottles. Each

Study Intervention(s)				
	wallet will be labeled as required per country requirement. Products will be provided with blinded labels.	blister wallets. Each wallet will be labeled as required per country requirement. Products will be provided with blinded labels.	bottle will be labeled as required per country requirement. Products will be provided with blinded labels.	bottle will be labeled as required per country requirement. Products will be provided with blinded labels.
Current/Former Name(s) or Alias(es)	PF-07321332	NA	ritonavir	NA

Study Arm(s)			
Arm Title	Nirmatrelvir/ritonavir 5-day	Nirmatrelvir/ritonavir 10-day	Nirmatrelvir/ritonavir 15-day
Arm Type	Experimental, placebo	Experimental, placebo	Experimental
Arm Description	Participants will receive nirmatrelvir/ritonavir 300 mg/100 mg (or 150 mg/100 mg for participants with eGFR ≥30 to <60 mL/min/1.73 m^2 or eCrCl ≥30 to <60 mL/min) q12h from Day 1 through Day 5 followed by placebo for nirmatrelvir/placebo for ritonavir q12h for Day 6 through Day 15.	Participants will receive nirmatrelvir/ritonavir 300 mg/100 mg (or 150 mg/100 mg for participants with eGFR ≥30 to <60 mL/min/1.73 m^2 or eCrCl ≥30 to <60 mL/min) q12h from Day 1 through Day 10 followed by placebo for nirmatrelvir/placebo for ritonavir q12h for Day 11 through Day 15.	Participants will receive nirmatrelvir/ritonavir 300 mg/100 mg (or 150 mg/100 mg for participants with eGFR ≥30 to <60 mL/min/1.73 m^2 or eCrCl ≥30 to <60 mL/min) q12h from Day 1 through Day 15.
Associated Intervention Labels	Nirmatrelvir/ritonavir (5-day)	Nirmatrelvir/ritonavir (10-day)	Nirmatrelvir/ritonavir (15-day)

Nirmatrelvir/ritonavir may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the nirmatrelvir/ritonavir. Pfizer does not permit the shipment of nirmatrelvir/ritonavir by mail. The tracking record of shipments, including temperature monitoring data, and the chain of custody of nirmatrelvir/ritonavir must be kept in the participant's source documents/medical records.

6.1.1. Administration

The first dose of study intervention will be administered at the site.

Nirmatrelvir 150 mg tablets or placebo for nirmatrelvir will be administered with ritonavir 100 mg or placebo for ritonavir capsules for 15 days. Participants will be dispensed 1 blister wallet card of nirmatrelvir 150 mg tablets and 1 bottle of ritonavir capsules at the Day 1 site visit. Participants will be dispensed 1 blister wallet card of nirmatrelvir 150 mg or placebo for nirmatrelvir tablets and 1 bottle of ritonavir capsules or placebo for ritonavir at the subsequent Day 5 and Day 10 visits. Participants will be instructed to take:

- 2 tablets of nirmatrelvir 150 mg or placebo for nirmatrelvir q12h;
- 1 capsule of ritonavir 100 mg or placebo for ritonavir q12h.
    - Participants with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2 or eCrCl ≥30 to <60 mL/min at screening) will receive either 1 tablet of nirmatrelvir 150 mg and placebo for nirmatrelvir or 2 tablets of placebo for nirmatrelvir (Section 6.6). The dose for ritonavir remains unchanged (ie, participants will receive 1 capsule of ritonavir 100 mg or placebo for ritonavir q12h).

Participants should take the first dose of study intervention on Day 1, during the in-person visit; that is, participants should take 2 tablets of nirmatrelvir 150 mg and 1 capsule of ritonavir 100 mg at the same time and no more than 15 minutes apart. The study intervention should be taken every 12 hours (±4 hours), but no more than twice in a calendar day. Timing of the second dose of nirmatrelvir/ritonavir may be adjusted slightly to allow participants to select a convenient 12-hour dosing schedule as long as the second dose is taken at least 4 hours but no later than 16 hours after the first dose. Once the dosing schedule is adjusted, subsequent doses should be taken every 12 hours (±4 hours).

If a dose is delayed, it should be taken as soon as possible, but no later than 4 hours before the next scheduled dose, and then resume the normal dosing schedule. If the participant misses a dose by more than 8 hours, the participant should not take the missed dose and instead take the next dose at the regularly scheduled time. The participant should not double the dose to make up for a missed dose. Dosing should be stopped at the end of the treatment period (30 doses total). Any remaining tablets and/or capsules at the Day 5, Day 10, and Day 15 visits should be returned.

Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing. Participants may take the study intervention with or without food. Taking study intervention with food may improve tolerability. Refer to the IPM for additional dosing and administration instructions.

6.2. Preparation, Handling, Storage, and Accountability

The excipients used in the nirmatrelvir tablets/ritonavir capsules are safe for administration to pediatric participants.

Study intervention will be self-administered by the pediatric participant or administered to the pediatric participant by the parent/caregiver.

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

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

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

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

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

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

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

form/record. All nirmatrelvir/ritonavir that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. **Returned study intervention must not be redispensed to the participants.**

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

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

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the nirmatrelvir/ritonavir using unique container numbers via an IRT system in the bottles and blister cards provided, in quantities appropriate according to the SoA. A second staff member will verify the dispensing. The participant/caregiver should be instructed to maintain the product in the bottle and blister cards, as provided throughout the course of dosing and return the bottle and blister cards, as appropriate to the site at the next study visit.

The study intervention will be administered in a blinded fashion to the participants.

6.3. Assignment to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned treatment group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

For the main study population, randomization will be stratified by participants who are considered immunocompromised solely based on corticosteroids or TNF blocker use (yes/no). Enrollment of participants who are considered immunocompromised solely based on corticosteroids or TNF blocker use will be capped at approximately 25% for the main study population.

Randomization for the population with rebound will not be stratified by those who are considered immunocompromised solely based on corticosteroids or TNF blocker use. Enrollment of participants considered immunocompromised based solely on receiving corticosteroids or TNF blockers in the additional population with rebound will not be capped.

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

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

Returned study intervention must not be redispensed to the study participants.

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

6.4. Blinding

This is a double-blind study.

6.4.1. Blinding of Participants

Participants and their caregivers will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention.

Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

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

6.4.3. Blinding of the Sponsor

Sponsor staff will be blinded to participants' assigned study intervention.

Sponsor staff who are not directly involved with the conduct of this study will prepare analyses and documentation containing unblinded data while the study is ongoing to support interactions with the E-DMC.

The study will be unblinded after all participants complete the Day 44 visit (or ET prior to Day 44 visit) and analyses through Day 44, including the primary efficacy endpoint analyses, will be conducted.

Details of the unblinded sponsor staff supporting the E-DMC and the timing of unblinding will be outlined in the Unblinding Plan.

6.4.4. Breaking the Blind

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

of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

6.5. Study Intervention Compliance

Participants will use a participant-completed electronic dosing diary to record the date and time of their study intervention dosing, and will be educated at the time of first dose.

Site personnel will review the participant-completed electronic dosing diary daily during the study intervention period, preferably after the participant has self-administered the morning dose of nirmatrelvir/ritonavir. If any noncompliance with dosing is suspected, site personnel will promptly contact the participant by phone, to remind them of the relevant study procedures and/or entering the information in the electronic diary as applicable.

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 of study intervention administered in the clinic will be recorded by the participant in the ediary. 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.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by delegated study personnel upon return of study intervention through counting returned tablets/capsules and direct questioning, if applicable during the site visits and documented in the source documents.

A record of the number of nirmatrelvir tablets/ritonavir capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

The following noncompliance cases will be considered medication errors (see Section 8.4.10).

- Participants interrupting study intervention for 2 consecutive doses;
- Participants taking either nirmatrelvir or ritonavir alone for 2 consecutive doses;
- Participants who have an overall study intervention compliance <80% or >115%.

In addition to the above listed-medication errors, any deviation from protocol-specified dosing (eg, missed single dose or partial dose) should be recorded as a protocol deviation and

the investigator or designee is to counsel the participant/guardian and ensure steps are taken to improve compliance.

6.6. Dose Modification

The dose may need to be modified on Day 5 or Day 10, based on the eGFR or eCrCl result from the point-of-care device:

- Participants with a Day 5 or Day 10 eGFR <60 mL/min/1.73 m^2 or eCrCl <60 mL/min will receive a wallet consisting of 1 tablet of nirmatrelvir 150 mg and placebo for nirmatrelvir or 2 tablets of placebo for nirmatrelvir. The dose of ritonavir remains unchanged.

- Participants with a Day 5 or Day 10 eGFR >60 mL/min/1.73 m^2 or eCrCl >60 mL/min, will receive a wallet consisting of 2 tablets of nirmatrelvir 150 mg or 2 tablets of placebo for nirmatrelvir. The dose of ritonavir remains unchanged.

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

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

Study sites should warn parents/caregivers to store the study intervention out of reach of children and to provide close supervision when intervention will be self-administered by the child.

For this study, any dose of nirmatrelvir/placebo greater than 900 mg (or any dose greater than 450 mg for participants on the reduced nirmatrelvir/placebo regimen) or ritonavir/placebo greater than 300 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis within 1 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

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

6.9. Prior and Concomitant Therapy

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

Prior Therapy

Use of an antiviral or monoclonal antibody therapy for the treatment of COVID-19 within 30 days prior to screening is prohibited, except for participants in the additional population with rebound, who must have completed a recent (ie, within 14 days) initial 5-day course of nirmatrelvir/ritonavir (see Section 10.9.5).

Permitted During the Study

Participants may receive concomitant medications, including SoC therapy for COVID-19, in addition to study intervention, unless listed as prohibited medication (see Appendix 8) or as defined in Section 5.2. However, use of antiviral therapy, including monoclonal antibody therapy, is prohibited through the entire treatment period, except for participants who progress to severe or critical COVID-19.[30]

SoC therapy is defined as any therapy that is approved and used as indicated by the local regulatory authorities (including approvals for emergency use, compassionate use, or through similar regulatory guidance), or any therapy as recommended by a relevant national (or a reputable international) scientific body (eg, WHO, ECDC, CDC, NIH).

Sites should consult with the sponsor if a new SoC option becomes available after study initiation. Investigator should ensure that any recommended SoC therapy is not a strong inducer of CYP3A4 or highly dependent on CYP3A4 for clearance.

Ritonavir is an inhibitor of CYP3A4 and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A4. Participants will receive ritonavir for at least 5 days and up to 15 days but as treatment is blinded, some concomitant medications (Appendix 8, Table 5) may require monitoring of drug levels, consideration of temporary withdrawal of the concomitant medication, or dose adjustment throughout the study treatment period and following completion of the blinded treatment duration period.

Prohibited During the Study

Use of a non-study antiviral or monoclonal antibody therapy for the treatment of COVID-19 within 15 days after randomization is prohibited, except for participants who progress to severe or critical COVID-19.[30]

Nirmatrelvir and ritonavir are both primarily metabolized by cytochrome P450 (CYP) 3A4. In addition, ritonavir is a strong inhibitor of CYP3A4. Therefore, concomitant use of medications that are strong inducers of CYP3A4 and which are contraindicated in combination with nirmatrelvir/ritonavir (see Appendix 8) are prohibited during study treatment.

Additionally, coadministration of nirmatrelvir/ritonavir with other medications that are not contraindicated but are highly dependent on CYP3A4 for clearance may require dose adjustment or additional monitoring. Investigators should reference Appendix 8 for a nonexhaustive list of these medications and consult the Pfizer medical monitor for guidance on coadministration with nirmatrelvir/ritonavir.

Medications or substances that are strong inducers of CYP3A4 and that are contraindicated in combination with nirmatrelvir/ritonavir must be discontinued for an appropriate washout period prior to the first dose of nirmatrelvir/ritonavir and are prohibited for the duration of the study treatment period and for 4 days after the last dose of nirmatrelvir/ritonavir (Appendix 8). The appropriate washout period for CYP3A4 inducers should be determined based on the prescribing information for the concomitant medication and in consultation with the medical monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- AE of Grade 3 severity or greater and considered by the investigator to be related to study intervention;
- SAE considered by the investigator to be related to study intervention;
- Requirement for prohibited concomitant medication;
- Participants who become pregnant during the course of the study;
- Study terminated by sponsor;
- Withdrawal by participant or legally authorized representative

- If post-screening eGFR <30 mL/min/1.73 m^2 or eCrCl is <30 mL/min the participant will be instructed to discontinue any remaining study intervention doses as soon as study staff become aware of the eGFR results.

In the event that a participant is hospitalized, study intervention may continue to be administered, as feasible, and based on medical judgment of the investigator.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for all subsequent scheduled assessments. 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 their own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Study terminated by sponsor;
- Withdrawal of consent/assent by parent/legal guardian or by a child who has provided assent during any phase of the study.

At the time of discontinuing from the study (if before Day 44), if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

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

If the participant withdraws from the study at any time and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed

and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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/assent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from 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 the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to be available for a required study visit:

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

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

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

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

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

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

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

The total blood sampling volume for individual adult participants in this study is approximately 260 mL. The total blood sampling volume for individual pediatric participants is approximately 195 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days. For pediatric participants, every effort will be made to ensure that blood volume collections do not exceed 1% of the total blood volume at any single time and 3% of the total blood volume during any period of 4 weeks.

8.1.1. Baseline Procedures

8.1.1.1. Medical History

Medical history in addition to COVID-19 disease history and demographics will be collected at screening. Smoking status will be collected. Complete medication history of all prescription or nonprescription drugs (including vaccinations), and dietary and herbal supplements taken within 30 days prior to the planned first dose will be collected. COVID-19-related vaccinations and monoclonal antibody treatment for the treatment of COVID-19 at any time prior to the planned first dose will also be collected.

Risk factors for the participant developing severe COVID-19 illness will be recorded.

8.1.1.2. Study Kit

The study kit includes the pulse oximeter that is to be used based on the instruction and medical judgement of the site investigator as well as dosing instructions.

8.1.1.3. Secondary Contacts

On Day 1 and at times specified in the SoA, the investigator will collect contact information for at least 2 individuals who can be contacted if the participant cannot be reached after multiple attempts (repeat/update as needed). Secondary contacts may be used to determine if a participant is lost to follow-up or for a vital status check.

8.1.2. Home Health Visits

A home health visit may be utilized to facilitate scheduled visits. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit (see the SoA):

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Collect clinical laboratory, PK, and biomarker samples.
- Collect NP swab samples.
- Collect vital signs.
- Confirm the participant has completed the PRO assessments.
- If the HCP is unable to collect AEs, concomitant medications or contraception use, the site should contact the participant via a follow-up telephone call to collect the additional information.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

8.1.3. Mobile Visits

In the event that an in-person visit is not feasible at the site, the following may be performed by a licensed healthcare professional at an alternate site approved by the investigator (see the SoA):

- Review and record study intervention(s), including compliance and missed doses.

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Collect clinical laboratory, PK, and biomarker samples.
- Collect NP swab samples.
- Collect vital signs.
- Confirm the participant has completed the PRO assessments.
- If the HCP is unable to collect AEs, concomitant medications or contraception use, the site should contact the participant via a follow-up telephone call to collect the additional information.

8.1.4. Telehealth Visits

Telehealth visits are not intended to replace in-person visits; however, may be used to assess participant safety and collect data points if an in-person visit is unable to be performed. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit (see the SoA):

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Collect vital signs (pulse and O_2 saturation using pulse oximeter device at home; temperature if available).

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

8.2. Efficacy Assessments

8.2.1. Participant Diary

Participants will be provided an electronic handheld device or will use their own device to record study intervention administration (as well as reason for changed or missed dose), signs and symptoms of COVID-19, and PRO assessments in the study diary.

Participants will receive daily reminders to complete entries on their own as specified in the SoA. The diary should be completed at approximately the same time every day. Staff will review the participant's study diary online as specified in the SoA.

The diary allows recording of these assessments only within a fixed time window (next calendar day), thus providing an accurate representation of the participant's experience at that time. The participant is able to make revisions to incorrect entries before pressing the save or submit button. In the event that a participant becomes aware of an error in data after the entry is saved, a change to the diary data may only be made by the investigator submitting a data clarification form. Data reported in the participant diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the sponsor or delegate at all times via an internet-based portal.

8.2.2. COVID-19-Related Hospitalizations and Medical Details

Details of participants' COVID-19-related medical visits (ie, hospitalization of any duration, urgent care, emergency room ≤24h) will be collected during study visits, including level of care (ICU status) and dates of utilization, including admission and discharge, as applicable.

Hospitalization >24 hours is defined as >24h of acute care in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19. This includes specialized acute medical care unit within an assisted living facility or nursing home. This does not include hospitalization for the purposes of public health and/or clinical trial execution.

8.2.3. Oxygen Support Details

Type of oxygen support (eg, oxygen supplementation received, mechanical ventilation or ECMO received in hospital) will be collected.

8.2.4. PRO Assessments

Only adult study participants ≥18 years of age at the time of screening will be asked to complete PRO assessments. PRO assessments will be recorded in the study ediary.

8.2.4.1. Global Impression Questions

Three questions will be included in the ePRO to assess patient-reported global impression items: a) return to usual health; b) return to usual activities; and c) overall COVID-19-related symptoms.[31]

8.2.4.2. SF-36 v2® Health Survey (Acute Form)

SF-36 v2® Health Survey (the acute form) is a 36-item questionnaire that measures functional health and well-being from a patient's perspective over 1-week recall period. It is a generic questionnaire and can be used across age (adults), disease, and treatment groups. The questionnaire consists of 8 health domain scales: physical functioning (10 items), role-physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role-emotional (3 items), mental health (5 items), reported health transition (1 item) and 2, physical and mental component summary scores. Each health domain scale raw score is transformed to 0-100 scale which can then be converted to norm-based T-scores (Mean=50, SD=10). SF-36 v2® Health Survey will be completed as specified in the SoA.

8.2.4.3. WPAI

COVID-19 impacts manual and office-based work, and results in missed work due to illness or quarantine and loss of productivity.[32] The WPAI-GH is being implemented for COVID-19 (ie, WPAI-COVID-19) in order to evaluate change from baseline in work burdens. The WPAI-GH has demonstrated validity, reliability and sufficient predictive value to measure the impact of disease on absenteeism, presenteeism, and overall productivity in a manner that can also be monetized. [33]

The WPAI-COVID-19 consists of 6 questions that refer to the following assessments for work productivity: 1 = currently employed, 2 = hours missed due to health problems, 3 = hours missed other reasons, 4 = hours actually worked, 5 = degree health affected productivity while working (using a 0 to 10 VAS), and 6 = degree health affected productivity in regular unpaid activities. The recall period for questions 2 through 6 is 7 days. Four main outcomes will be generated from the WPAI-COVID-19 and reported as: 1) percent work time missed due to COVID-19 for those who are currently employed, 2) percent impairment while working due to COVID-19 for those who are currently employed and actually worked in the past 7 days, 3) percent overall work impairment due to COVID-19 for those who are currently employed, and 4) percent activity impairment due to COVID-19 for all respondents.[33] The WPAI-COVID-19 will be completed during site visits, as specified in the SoA.

8.2.4.4. EQ-5D-5L Scale

The EQ-5D is a validated, standardized, generic instrument that is a preference-based health related quality of life questionnaire in cost effectiveness and HTA.[34-36] Recently, a version was developed called EQ-5D-5L with 5 response levels on each dimension compared to the 3 response levels in the EQ-5D-3L.[34-40]

Measurement properties of the EQ-5D-5L demonstrated to be a valid version of the 3 level questionnaire that improved measurements by adding discriminatory power, reducing the ceiling, and establishing convergent and known groups validity.[34,36,38,39] Both the EuroQol EQ-5D-3L and EQ-5D-5L versions are well established instruments used to measure health states and utilities in various diseases areas and assess mobility, self care, usual activities,

pain/discomfort, anxiety/depression and health status using a VAS[37,41] The EQ-5D-5L should be completed as described in the SoA.

8.2.5. COVID-19 Signs and Symptoms

On Day 1, participants will complete the COVID-19 signs and symptoms (Appendix 10) in the study diary, before receiving study intervention. COVID-19-related symptoms will be evaluated in accordance with FDA guidelines. Participants will record a rating of their symptom severity over the past 24 hours based on a 4-point scale in which 0 is reported if no symptoms were present; 1 if mild; 2 if moderate; and 3 if severe.

Vomiting and diarrhea will each be rated on a 4-point frequency scale where 0 is reported for no occurrence, 1 for 1 to 2 times, 2 for 3 to 4 times, and 3 for 5 or greater.

Sense of smell and sense of taste will each be rated on a 3-point Likert scale where 0 is reported if the sense of smell/taste was the same as usual, 1 if the sense of smell/taste was less than usual, and 2 for no sense of smell/taste.

8.3. Safety Assessments

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

8.3.1. Targeted Physical Examinations

Physical examinations to be completed before administration of study intervention.

A targeted physical examination will include, at a minimum, cardiopulmonary assessments. Investigators should pay special attention to any previously identified or new AE/targeted condition that the participant has experienced. Height and weight will also be measured and recorded at screening, though height may be self-reported for participants ≥18 years of age.

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

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

8.3.2. Vital Signs

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

Temperature, pulse rate, respiratory rate, oxygen saturation level, and blood pressure will be assessed as specified in the SoA.

8.3.2.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with the participant, preferably in the supine or seated position with their feet on the floor when possible with a completely automated device.[42] It is recommended that the same position should be used for a participant throughout the study duration. Manual techniques will be used only if an automated device is not available.

8.3.2.2. Temperature and Respiratory Rate

Temperature, and respiratory rate, will be assessed.

8.3.2.3. Oxygen Saturation Level

Oxygen saturation level will be assessed as part of the vital signs assessment.

8.3.2.4. At-Home Devices for Vital Signs

Each participant will also be supplied with a pulse oximeter to be used based on the instruction and medical judgment of the site investigator.

8.3.3. Point-of-Care Serum Creatinine Assessments

A serum creatinine point-of-care device will be used to assess kidney function as described in the SoA and Appendix 2.

8.3.4. Clinical Safety Laboratory Assessments

Laboratory safety parameters will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events[43], version 2.1. 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 significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that 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 significant and 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 study 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 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

8.3.5. Pregnancy Testing

A serum or urine pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at Day 44 or ET visit. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

For female pediatric participant who becomes pregnant, this information will be shared with the study participant's parent/guardian if the participant's age is within specific range based on local/country regulations.

8.3.5.1. At-Home Pregnancy Testing

A home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

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

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally

authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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

During the active collection period as described in Section 8.4.1, each participant/parent/legal guardian/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

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

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

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

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

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

After the defined active collection period for safety events, long-term follow-up visits are also conducted at Weeks 12 and 24. Any new SAE occurring during this long-term follow-up period and determined to be related to study intervention must be reported to Pfizer Safety immediately upon awareness and under no circumstance should this exceed 24 hours.

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

including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the PSSA.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety using PSSA immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications

and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be newly pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:

- A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.

- A male family member or healthcare provider who has been exposed to the study intervention by ingestion then inseminates his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant or participant's partner, the investigator must report this information to Pfizer Safety using the EDP Supplemental form within PSSA, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until a minimum of 28 calendar days after the last administration of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed case report from PSSA 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 using PSSA. 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 in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as

SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion.

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. 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.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported Using the PSSA to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	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.

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.

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

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

8.5. Pharmacokinetics

A blood sample of approximately 1 mL, to provide approximately 0.5 mL plasma, will be collected for measuring plasma concentrations of nirmatrelvir and ritonavir (if feasible) as specified in the SoA.

Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of the baseline sample obtained <30 min later than the 1-2 hour post-dose timepoint will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation does not apply to samples that are specified to be collected “at any time”.

PK samples may be collected at any time during the visit on Days 5, 10, and 15. PK samples collected within the allowed visit window schedule will not be captured as a protocol deviation.

Samples collected for analyses of ninnatrelvir and ritonavir concentrntions may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanal ical method or for research related to the stud intervention s and COVID-19 CCI [redacted]

If a participant cannot attend in-clinic visits, PK samples may be collected via home health or mobile visit. The time of PK samples being taken will be recorded.

Genetic analyses will not be perfo1med on these plasma samples unless consent for this was included in the infonned consent. Paiiicipant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of study intervention will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or explorato1y methods.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented, and reported to the sponsor. On a case-by-case basis, the sponsor may make a detennination as to whether sample integrity has been compromised.

Dmg concenti·ation info1mation that would unblind the study will not be repo1ied to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then ai·chived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be infonned of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

Retained Reseai·ch Samples will be collected from adult paiiicipants only; these samples will not be collected from participants who ai·e under the age of 18 at the time of enrollment.

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s) and COVID-19. Genes and other analytes (eg, proteins, RNA, nondmg metabolites) may be studied using the retained samples.

See Appendix 5 for info1mation regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laborato1y manual.

8.7. Biomarkers

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected in this study as specified in the SoA:

CCI

Residuals of all samples may be stored for future research. Storage and shipping instructions will be in accordance with the laborato1y manual.

CCI

Residuals of all samples may be stored for future research. Storage and shipping instructions will be in accordance with the laborato1y manual.

CCI [redacted]

Details on processes for collection and shipment of these samples can be found in the laboratory manual and supporting documents.

8.7.6. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.7. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

- CCI [redacted]

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA. Retained Research Samples will be collected from adult participants only; these samples will not be collected from participants who are under the age of 18 at the time of enrollment.

Retained Research Samples may be used for research related to the study intervention(s) and COVID-19. Genes and other analytes (eg, proteins, RNA, nondmg metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters will be evaluated for this study (Section 8.2.2 and Section 8.2.4).

9. STATISTICAL CONSIDERATIONS

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

The efficacy and safety data will be analyzed and summarized separately for the main study population and the additional population with rebound. Further details on the analyses planned for the additional population with rebound will be included in the SAP.

There will be 2 analysis time points for reporting the results of this study. The primary analysis will be performed after all participants in the main study population have completed the Day 44 visit. The follow-up analysis will be performed after all participants in the main study population have completed the Week 24 visit. In addition, both analyses (primary and follow-up) will include separate results for the main study population and the additional population with rebound.

9.1. Statistical Hypotheses

No formal hypothesis testing will be performed for this study.

9.1.1. Estimands

9.1.1.1. Primary Estimand/Coprimary Estimands

The primary estimand, reported separately for the main study population and the population with rebound, is the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 in nonhospitalized, symptomatic patients ≥12 years of age with COVID-19 who are immunocompromised. This will be estimated without regard to study treatment discontinuation and considering participants receiving non-study antiviral or monoclonal antibody therapy post-baseline for the treatment of COVID-19 as not achieving sustained NP swab SARS-CoV-2 RNA <LLOQ.

9.1.1.2. Secondary Estimands

Not Applicable.

9.1.2. Multiplicity Adjustment

There will be no adjustment for multiplicity.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined and will be applied for the main study population and the population with rebound:

Participant Analysis Set	Description
Full analysis set	All participants randomly assigned to study intervention.
Evaluable analysis set/Safety Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.

The evaluable analysis set will be the primary analysis set for evaluating the primary estimand.

9.3. Statistical Analyses

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

9.3.1. General Considerations

Descriptive statistics for all endpoints will be provided by treatment arm.

The number of participants screened, completing the study drug administration, and completing the study will be summarized. The reason for all discontinuations will be summarized.

Baseline demographic and other characteristics will be tabulated for the FAS.

For continuous endpoints, descriptive statistics for change from baseline will be provided.

For binary endpoints, the proportion of participants with the event will be summarized.

For categorical endpoints, the proportion of participants for each category will be summarized.

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

9.3.2.1. Definition of Endpoint(s)

The primary endpoint, summarized separately for the main study population and the population with rebound, is the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44.

Sustained is defined as NP swab SARS-CoV-2 RNA level not ≥2.0 $\log_{10}$ copies/mL at any study visit (through Day 44) following the first study visit where the participant's NP swab SARS-CoV-2 RNA <LLOQ.

9.3.2.2. Main Analytical Approach

The primary descriptive analysis will summarize, separately for the main study population and the population with rebound, the number and proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 for each treatment arm in the Evaluable Analysis Set and FAS. Participants receiving non-study antiviral or monoclonal antibody therapy post-baseline for the treatment of COVID-19 will be considered as not achieving sustained NP swab SARS-CoV-2 RNA <LLOQ in the primary analysis. In addition, 95% CIs for the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ from Day 15 through Day 44 for each treatment arm will be calculated. The difference in proportions for the primary endpoint and associated 95% CI will be calculated for each pairwise comparison of the treatment arms.

9.3.2.3. Supplementary Analysis/Analyses

Supplemental analyses will be performed for the primary efficacy endpoint:

1. An analysis of the primary endpoint will be conducted excluding data after the date of non-study antiviral or monoclonal antibody start for participants receiving non-study antiviral or monoclonal antibody therapy post-baseline for the treatment of COVID-19.

2. An analysis of the primary endpoint will be conducted to include all NP swab SARS-CoV-2 RNA data regardless of whether participants received non-study antiviral or mAb treatment post-baseline for the treatment of COVID-19.

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

Details on the definitions and analyses of secondary endpoints will be described in the SAP. Secondary endpoints include:

- Time to first NP swab SARS-CoV-2 RNA<LLOQ (<2.0 $\log_{10}$ copies/mL) for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline.

- Time to sustained NP swab SARS-CoV-2 RNA <LLOQ (<2.0 $\log_{10}$ copies/mL) through Day 44 for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline.

- Proportion of participants with SARS-CoV-2 RNA <LLOQ in plasma over time.
- Proportion of participants with SARS-CoV-2 RNA level in NP swabs <2.0 $\log_{10}$ copies/mL at each study visit through Day 44.
- Change from baseline in SARS-CoV-2 RNA level in NP swabs and in plasma over time.
- Rebound in SARS-CoV-2 RNA level in NP swabs at follow up (ie, any study visit after end of treatment through Day 44) that is defined as a half (0.5) $\log_{10}$ copies/mL increase or greater in SARS-CoV-2 RNA level relative to end of treatment SARS-CoV-2 RNA level based on treatment regimen, with a follow-up viral RNA level ≥2.5 $\log_{10}$ copies/mL.
- Incidence of TEAEs.
- Incidence of SAEs and AEs leading to discontinuations.
- Proportion of participants with COVID-19-related hospitalization >24 hours, or death from any cause through Day 28.
- Proportion of participants with death (all cause) through Week 24.
- Proportion of participants with COVID-19-related hospitalization of any duration.
- Proportion of participants with COVID-19-related ICU admission of any duration.
- Proportion of participants requiring invasive mechanical ventilation or ECMO.
- Number of days in hospital and ICU stay in participants with COVID-19-related hospitalization.
- Number of COVID-19-related medical visits through Day 44 and through Week 24.
- Duration of each targeted COVID-19 signs/symptoms.
- Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 44.
- Nirmatrelvir and ritonavir PK in plasma and whole blood (if feasible).

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

- Not applicable.

9.3.5. Safety Analyses

All safety analyses will be performed on the safety analysis set.

9.3.6. Other Analyses

Pharmacogenomic and/or biomarker data from samples collected as described in the SoA, as well as Retained Research Samples may be retained for future analyses; the results of such analyses are not planned to be included in the CSR.

Rates of detection of cell culture infectious virus over time will be characterized during the trial and will be reported in a separate report outside of the CSR.

PRO data (SF-36, WPAI, EQ-5D-5L, and global impression questions) will be collected during the trial and are not planned to be included in the CSR.

Results from population PK analyses will be reported in a separate report outside of the CSR.

9.4. Interim Analyses

No formal interim analysis will be conducted for this study.

9.5. Sample Size Determination

Up to approximately 200 participants will be enrolled in this study.

The study will randomize approximately 150 participants in a 1:1:1 randomization ratio, resulting in approximately 50 participants in each treatment arm (main study population). In addition, the study will also enroll up to 50 additional nonhospitalized symptomatic participants (in a 1:1:1 randomization ratio) who are immunocompromised with a rebound in COVID-19 within 14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir (population with rebound).

Analyses will be conducted after the main study population is fully enrolled and have completed the Day 44 visit regardless of the number of randomized participants in the population with rebound. There will be 2 analysis time points for reporting the results of this study. The primary analysis will be performed after all participants in the main study population have completed the Day 44 visit. The follow-up analysis will be performed after all participants in the main study population have completed the Week 24 visit. In addition, both analyses (primary and follow-up) will include separate results for the main study population and the additional population with rebound.

As no formal hypothesis testing will be performed for this study, no power calculation was carried out to assess the number of participants required for each treatment arm. For the main study population, the goal of the primary analysis is to estimate the treatment effect for each duration of nirmatrelvir/ritonavir. The smaller numbers of participants in these groups will be reflected in the precision of the estimate of the primary endpoint. Table 2 displays which effect sizes would be excluded based on the expected width of the confidence interval around the estimate of the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 with a sample size of 50.

When the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ from Day 15 through Day 44 ranges from 0.1 to 0.5, Table 2 displays the precision (width of the confidence interval) for the respective proportion to be estimated with a sample size of 50. That is, the width of the 95% CI does not exceed 14%.

Table 2. Width of 95% CI for the Proportion of Participants with Sustained NP Swab SARS-CoV-2 RNA <LLOQ

Nirmatrelvir/Ritonavir (n=50)	
Proportion of Participants With Sustained Viral RNA level <LLOQ	**Width of CI**
0.1	0.083
0.2	0.111
0.3	0.127
0.4	0.136
0.5	0.139

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new

information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent/Assent Process

10.1.3.1. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative 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 legally authorized representative (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

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

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

10.1.3.2. Informed Assent Process

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

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

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

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

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

The participant's parent(s)/legal guardian must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s)/legal guardian.

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

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

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

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

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

10.1.4. Data Protection

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

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

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

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

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

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.8. Source Documents

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

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

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

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

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

10.1.9. 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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory

requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

10.1.10. Publication Policy

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

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

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

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

10.1.11. Sponsor's Medically Qualified Individual

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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.

If deemed necessary to confirm eligibility, additional laboratory assessments at screening may be performed at the local laboratory at the investigator's discretion.

Table 3. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Other	Reflex Testing:
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea Creatinine eGFR or CrCl[a], Sodium Potassium AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein Glucose (random) Calcium Chloride Total CO_2 (bicarbonate) **Renal Function for Eligibility and Determination of Dosing:** eGFR or eCrCl will be assessed from creatinine value that will be obtained from a point-of-care device provided by the sponsor at screening (and also at baseline if screening and baseline visits are held on different days). An additional assessment may be performed on Day 5 or Day 10 at the investigator's discretion	At screening only: FSH[b] As per Schedule of Activities: Pregnancy test (β-hCG)[c] **Thyroid function** TSH T4 (free) **Viral Serology** SARS-CoV-2	For suspected DILI: AST/ALT Total bilirubin, direct and indirect bilirubin Total bile acids, GGT Total protein, albumin CK PT, INR Acetaminophen/paracetamol or protein adduct levels Hepatitis serology

a. eGFR will be calculated using the method developed by the CKD-EPI for participants 18 years or older or eCrCl using the Cockcroft-Gault formula for participants 12 years to <18 years
b. FSH testing is performed locally when needed to confirm postmenopausal status at screening.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occunence in a patient or clinical study paiiicipant, 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 abno1mal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

• Any abno1mal laborato1y test results (hematology, clinical chemistiy, 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 abno1mal laborato1y 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 medicaVsurgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional conc01nitant drng ti·eatment, or other therapy.
 	
• Exacerbation of a chronic or inte1mittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention adtninisti·ation, even though it may have been present before the staii of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected dtug-dtug 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 repo1ied as an AE or SAE unless it is an intentional overdose taken with possible suicidaVself-haiming intent. Such overdoses should be repo1ied regardless of sequelae.

Events Meeting the AE Definition
• Any clinically significant abno1mal laborato1y findings or other abno1mal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the paiticipant'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 paiticipant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untowai·d medical occunence 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 stait of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is **life-threatening** The te1m "life-threatening" in the definition of "serious" refers to an event in which the paiticipant 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 paiticipant has been admitted (usually involving at least an overnight stay) at the hospital or emergency wai·d for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization ai·e AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occuned or was necessaiy, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The te1m disability means a substantial disrnption of a person's ability to conduct nonnal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diaiThea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent eve1yday life functions but do not constitute a substantial disrnption.

e. **Is a congenital anomaly/birth defect**

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

The event may be suspected from clinical symptoms or laborato1y findings indicating an infection in a pa1ticipant exposed to a Pfizer product. The tenns "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by phaimacovigilance personnel. Such cases ai·e also considered for repo1ting as product defects, if appropriate.

g. **Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE repo1ting is appropriate in other situations, such as significant medical events that may jeopardize the paiticipant 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 diug dependency or diug abuse.

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for repo1ting SAEs using PSSA to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

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

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the PSSA; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using PSSA.
** **EDB** is reported to Pfizer Safety using the PSSA, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the PSSA.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of PSSA/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical info1mation. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories, which are based on the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events[43], version 2.1 (July2017):

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	POTENTIALLY LIFE-THREATENING event
5	DEATH RELATED TO adverse event

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occunence of each AE or SAE. The investigator will use clinical judgment to dete1mine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be rnled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product info1mation, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occmTed and the investigator has minimal info1mation to include in the initial repo1i to the sponsor. However, **it is**

very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change their opinion of causality in light of follow-up info1mation and send an SAE follow-up repo1t with the updated causality assessment.
- The causality assessment is one of the criteria used when dete1mining regulato1y repo1ting 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 repo1ting pmposes, as defined by the sponsor. In addition, if the investigator detennines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and repo1t such an assessment in the dedicated section of PSSA and in accordance with the SAE repo1ting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perfonn or aiTange 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 laborato1y tests or investigations, histopathological exaininations, or consultation with other healthcai·e providers.
- If a paiticipant dies during pa1ticipation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmo1tem findings, including histopathology.
- New or updated infonnation will be recorded in the originally submitted documents.
- The investigator will subinit any updated SAE data to the sponsor within 24 hours of receipt of the info1mation.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primaiy mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eSAE or PSSA).

- If the electronic system is unavailable, then the site will use the paper fonn (see next section) to repo1i the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper f01m (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entiy of new data or changes to existing data.
- If a site receives a repo1i of a new SAE from a study paiiicipant or receives updated data on a previously repo1ied SAE after the electi·onic DCT has been taken off-line, then the site can report this infonnation on a paper SAE fonn (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile ti-ansmission of the CT SAE Repo1i Fo1m is the prefened method to ti·ansrnit this infonnation to Pfizer Safety.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transpo1i Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Repo1i Fo1m sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Repo1i Fo1m pages within the designated repo1iing time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100 fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

- A female participant is eligible to participate if at least 1 of the following conditions applies:
  - Is not a WOCBP (see definition in Section 10.4.3).
    - OR
  - Is a WOCBP who is pregnant (at least 14 weeks gestation).
    - OR
  - Is a WOCBP who is not pregnant at screening and agrees to use a highly effective contraceptive method (failure rate of <1% per year) 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 any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

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

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

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

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 50 years of age and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

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

Highly Effective Methods That Are User Dependent

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

    - Oral + barrier*

    - Intravaginal + barrier*

    - Transdermal + barrier*

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

    - Oral + barrier*

    - Injectable + barrier*

Sexual Abstinence

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

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

- Male or female condom, with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

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

Because ritonavir may reduce the effect of estradiol-containing contraceptives when agents are co-administered, a barrier method or other nonhormonal method of contraception must

also be used if the participant is using estradiol-containing contraceptives during the 15 days of treatment and until 1 menstrual cycle after stopping study intervention.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to nirmatrelvir/ritonavir or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Retained samples will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

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

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: Age-Specific Kidney Function Calculation Recommendations

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

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

Inker LA et al. N Engl J Med. 2021;385:1737-49.[44]

10.7.1.1. Adolescents (12 Years to <18 Years)—Cockcroft-Gault Formula

CrCl (mL/min)

Males: Cr/Cl = [(140 – age) × body weight (in kg)] / [Scr (in mg/dL) × 72]

Females: Cr/Cl = 0.85 × [(140 – age) × body weight (in kg)] / [Scr (in mg/dL) × 72]

10.7.2. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

10.8. Appendix 8: Prohibited Concomitant Medications That May Result in DDI

Nirmatrelvir and ritonavir are both primarily metabolized by CYP3A4. Therefore, concomitant use of any medications or substances that are strong inducers of CYP3A4 and that are contraindicated in combination with nirmatrelvir/ritonavir are prohibited without the appropriate washout prior to the first dose of study intervention.

A nonexhaustive list of prohibited and precautionary medications is provided below (Table 4 and Table 5). If a medication is not listed as contraindicated, it should not automatically be assumed it is safe to coadminister. Appropriately qualified site staff will review all concomitant medications to determine if they are prohibited. The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the study intervention may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Table 4 and Table 5 list clinically significant drug interactions, with Table 4 listing the drugs contraindicated for use with nirmatrelvir/ritonavir. The drugs listed in Table 4 and Table 5 are a guide and not considered a comprehensive list of all possible drugs that may interact with nirmatrelvir/ritonavir. The healthcare provider should consult appropriate references such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir.

Table 4. Drugs That are Contraindicated With Nirmatrelvir/Ritonavir

Drug Class	Drugs Within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions.
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic

Table 4. Drugs That are Contraindicated With Nirmatrelvir/Ritonavir

Drug Class	Drugs Within Class	Effect on Concentration	Clinical Comments
			response and possible resistance.
Anticonvulsants	carbamazepine, phenobarbital, primidone, phenytoin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antimycobacterial	rifampin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered.
Antipsychotics	lurasidone, pimozide	↑ lurasidone ↑ pimozide	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias.
Benign prostatic hyperplasia agents	silodosin	↑ silodosin	Co-administration contraindicated due to potential for postural hypotension.
Cardiovascular agents	eplerenone	↑ eplerenone	Co-administration with eplerenone is contraindicated due to potential for hyperkalemia.
	ivabradine	↑ ivabradine	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot

Table 4. Drugs That are Contraindicated With Nirmatrelvir/Ritonavir

Drug Class	Drugs Within Class	Effect on Concentration	Clinical Comments
			toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance.
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of nirmatrelvir/ritonavir, during nirmatrelvir/ritonavir treatment duration, and for 5 days after completing nirmatrelvir/ritonavir.
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration contraindicated due to potential for acute and/or chronic nephrotoxicity.
Microsomal triglyceride transfer protein inhibitor	lomitapide	↑ lomitapide	Co-administration contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions.
Migraine medications	eletriptan ubrogepant	↑ eletriptan ↑ ubrogepant	Co-administration of eletriptan within at least 72 hours of nirmatrelvir/ritonavir is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events. Co-administration of ubrogepant with nirmatrelvir/ritonavir is contraindicated due to

Table 4. Drugs That are Contraindicated With Nirmatrelvir/Ritonavir

Drug Class	Drugs Within Class	Effect on Concentration	Clinical Comments
			potential for serious adverse reactions.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia.
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms
Pulmonary hypertension agent (PDE5 inhibitor)	sildenafil (Revatio®) when used for pulmonary arterial hypertension	↑ sildenafil	Co-administration contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope.
Sedative/hypnotics	triazolam, oral midazolam	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression.
Serotonin receptor 1A agonist/serotonin receptor 2A antagonist	flibanserin	↑ flibanserin	Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression.
Vasopressin receptor antagonists	tolvaptan	↑ tolvaptan	Co-administration contraindicated due to potential for dehydration, hypovolemia and hyperkalemia.

Table 5. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	tamsulosin	↑ tamsulosin	Avoid concomitant use with nirmatrelvir/ritonavir.

Table 5. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antiarrhythmics	lidocaine (systemic), disopyramide	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
Anticoagulants	warfarin	↑↓ warfarin	Closely monitor INR if co-administration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
	dabigatran	↑ dabigatran	Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information.
	apixaban	↑ apixaban	Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with nirmatrelvir/ritonavir depend on the apixaban dose. Refer to the apixaban product label for more information.

Table 5. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticonvulsants	clonazepam	↑ anticonvulsant	A dose decrease may be needed for clonazepam when co-administered with nirmatrelvir/ritonavir and clinical monitoring is recommended.
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole,	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate, itraconazole	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir/ritonavir	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
Anti-HIV protease inhibitors	atazanavir, darunavir, tipranavir	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased nirmatrelvir/ritonavir or protease inhibitor adverse events.
Anti-HIV	efavirenz, maraviroc, nevirapine, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↑ nevirapine ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.

Table 5. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.
Antimycobacterial	bedaquiline	↑ bedaquiline	Refer to the bedaquiline product label for further information.
	rifabutin	↑ rifabutin	Refer to rifabutin product label for further information on rifabutin dose reduction.
	rifapentine	↓ nirmatrelvir/ritonavir	Avoid concomitant use with nirmatrelvir/ritonavir.
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.
	clozapine	↑ clozapine	If co-administration is necessary, consider reducing the clozapine dose and monitor for adverse reactions.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with nirmatrelvir/ritonavir. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering nirmatrelvir/ritonavir with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.

Table 5. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Cardiovascular agents	aliskiren, ticagrelor, vorapaxar clopidogrel cilostazol	↑ aliskiren ↑ ticagrelor ↑ vorapaxar ↓ clopidogrel active metabolite ↑ cilostazol	Avoid concomitant use with nirmatrelvir/ritonavir. Dosage adjustment of cilostazol is recommended. Refer to the cilostazol product label for more information.
Corticosteroids primarily metabolized by CYP3A	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone	↑ corticosteroid	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A inhibitor is low. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone should be considered.
Cystic fibrosis transmembrane conductance regulator potentiators	ivacaftor elexacaftor/tezacaftor/ivacaftor tezacaftor/ivacaftor	↑ ivacaftor ↑ elexacaftor/tezacaftor/ivacaftor ↑ tezacaftor/ivacaftor	Reduce dosage when co-administered with nirmatrelvir/ritonavir. Refer to individual product labels for further information.
Dipeptidyl peptidase 4 inhibitors	saxagliptin	↑saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin product label for more information.
Endothelin receptor antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of nirmatrelvir/ritonavir. Refer to the bosentan product label for further information.

Table 5. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Hepatitis C direct acting antivirals	elbasvir/grazoprevir, glecaprevir/pibrentasvir	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. Avoid concomitant use of glecaprevir/pibrentasvir with nirmatrelvir/ritonavir.
	ombitasvir/paritaprevir/ritonavir and dasabuvir		Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information.
	sofosbuvir/velpatasvir/voxilaprevir		Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased nirmatrelvir/ritonavir or HCV drug adverse events with concomitant use.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with nirmatrelvir/ritonavir. Atorvastatin and rosuvastatin do not need to be held prior to or after completing nirmatrelvir/ritonavir.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during nirmatrelvir/ritonavir treatment and until one menstrual cycle after stopping nirmatrelvir/ritonavir.
Immunosuppressants	cyclosporine, tacrolimus	↑ cyclosporine ↑ tacrolimus	Avoid use of nirmatrelvir/ritonavir when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose

Table 5. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			adjustment of the immunosuppressant and monitoring for immunosuppressant concentrations and immunosuppressant-associated adverse reactions is recommended. Refer to the individual immunosuppressant product label for further information and obtain expert consultation from the patient's immunosuppressive therapy specialist.
	everolimus, sirolimus	↑ everolimus ↑ sirolimus	Avoid concomitant use of everolinus and sirolimus and nirmatrelvir/ritonavir.
Janus kinase (JAK) inhibitors	tofacitinib	↑ tofacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib product label for more information.
	upadacitinib	↑ upadacitinib	Dosage recommendations for co-administration of upadacitinib with nirmatrelvir/ritonavir depends on the upadacitinib indication. Refer to the upadacitinib product label for more information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Avoid concomitant use with nirmatrelvir/ritonavir. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Migraine medications	rimegepant	↑ rimegepant	Avoid concomitant use with nirmatrelvir/ritonavir.
Muscarinic receptor antagonists	darifenacin	↑ darifenacin	The darifenacin daily dose should not exceed 7.5 mg when co-administered with nirmatrelvir/ritonavir. Refer to the darifenacin product label for more information.

Table 5. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Narcotic analgesics	fentanyl, hydrocodone, oxycodone, meperidine	↑ fentanyl ↑ hydrocodone ↑ oxycodone ↑ meperidine	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone, oxycodone, or meperidine is concomitantly administered with nirmatrelvir/ritonavir. If concomitant use with nirmatrelvir/ritonavir is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
Neuropsychiatric agents	Suvorexant	↑ suvorexant	Avoid concomitant use of suvorexant with nirmatrelvir/ritonavir.
	aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin	↑ aripiprazole, ↑ brexpiprazole, ↑ cariprazine, ↑ iloperidone, ↑ lumateperone, ↑ pimavanserin	Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to individual product label for more information.
Pulmonary hypertension agents (PDE5 inhibitors)	tadalafil (Adcirca®)	↑ tadalafil	Avoid concomitant use with nirmatrelvir/ritonavir.
Pulmonary hypertension agents (sGC stimulators)	riociguat	↑ riociguat	Dosage adjustment is recommended for riociguat. Refer to the riociguat product label for more information.

Table 5. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Erectile dysfunction agents (PDE5 inhibitors)	avanafil	↑ avanafil,	Do not use nirmatrelvir/ritonavir with avanafil because a safe and effective avanafil dosage regimen has not been established.
	sildenafil, tadalafil, vardenafil	↑ sildenafil, ↑ tadalafil, ↑ vardenafil	Dosage adjustment is recommended for use of sildenafil, tadalafil, or vardenafil with nirmatrelvir/ritonavir. Refer to individual product labels for more information.
Sedative/hypnotics	buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑sedative/hypnotic	A dose decrease may be needed for these drugs when co-administered with nirmatrelvir/ritonavir and monitoring adverse events
	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.

10.9. Appendix 9: Eligibility Criteria

10.9.1. Age and Sex

Inclusion Criterion #1: Participants aged 12 years or older and weighing ≥40 kg at screening:

- Participants 12 years of age or older at the time of signing the informed consent. Adolescent participants below the age of 18 years (or country-specific age of majority) will only be enrolled if approved by the country regulatory/health authority. If these approvals have not been granted, only participants 18 years of age (or country-specific age of majority) or older at the time of signing of informed consent may be enrolled.

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

10.9.2. Confirmed SARS-CoV-2 Infection Details for the Main Study Population

Inclusion Criterion #2: Confirmed SARS-CoV-2 infection as determined by RT-PCR or other acceptable test method in any specimen collected within 5 days prior to randomization for the main study population.

Note: RT-PCR is the preferred method; however, with evolving approaches to confirmation of SARS-CoV-2 infection, other molecular or antigen tests that detect viral RNA or protein are allowed. The test result must be available to confirm eligibility. Participants may be enrolled based on positive results of a rapid SARS-CoV-2 antigen test performed at screening.

10.9.3. Signs and Symptoms Attributable to COVID-19

Inclusion Criterion #3: ≥1 sign/symptom attributable to COVID-19 present on the day of randomization (Appendix 10).

10.9.4. Immunocompromised Criteria Details

Inclusion Criterion #4: Immunocompromised with ≥1 of the following:

1. Solid organ (eg, liver, heart, lung or kidney) transplant recipient who is receiving immunosuppressive therapy;
2. Receipt of CAR-T-cell therapy or HCT either within 2 years of transplantation or who are receiving immunosuppressive therapy;
3. Moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome);
4. Use of at least 1 of the following immune-weakening medications:
    a. Recent treatment with corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days, all of which must have been within the last 30 days prior to study entry OR are currently receiving ≥20 mg daily that must have been administered for at least 14 consecutive days at the time of study entry.

b. Active treatment causing significant immunosuppression, including alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, TNF blockers, or other highly immunosuppressive drugs such as biologics (eg, ustekinumab, anti-CD20).

5. Active immunosuppressive treatment for solid tumor or hematological malignancy (including leukemia, lymphoma, and myeloma).
6. HIV infection with CD4 cell count <200 mm^3 from known medical history within the past 6 months of screening.

10.9.5. Inclusion Criteria for Additional Population With COVID-19 Rebound

Inclusion Criterion #2: Confirmed SARS-CoV-2 infection as determined by RT-PCR or rapid antigen testing in any specimen collected within 24h prior to randomization and collected within 14 days after the completion of the initial 5-day treatment course of nirmatrelvir/ritonavir.

Note: RT-PCR is the preferred method; however, with evolving approaches to confirmation of SARS-CoV-2 infection, other molecular or antigen tests that detect viral RNA or protein are allowed. The test result must be available to confirm eligibility. Participants may be enrolled based on positive results of a rapid SARS-CoV-2 antigen test performed at screening.

Inclusion Criterion #5: Presenting with documented, symptomatic, COVID-19 rebound within 14 days following completion of an initial 5-day treatment course with nirmatrelvir/ritonavir, defined as:

1. Participants must have written documentation, such as electronic health record, medical record, or prescription receipt of treatment with nirmatrelvir/ritonavir (verbal assertion of treatment is not acceptable) with patient-reported 100% compliance (ie, completed a 5-day course of nirmatrelvir/ritonavir). They must have symptom alleviation or resolution in COVID-19 signs/symptoms followed by a worsening (rebound) of signs/symptoms after completing an initial 5-day course of nirmatrelvir/ritonavir based on the judgement of both the participant and investigator.

2. The onset of rebound in COVID-19 symptoms must occur within 14 days after the completion of the initial 5-day course of nirmatrelvir/ritonavir.

3. Onset of signs/symptoms attributable to rebound COVID-19 within 48 hours prior to randomization and ≥1 sign/symptom to COVID-19 present on the day of randomization.

10.9.6. Oxygen Saturation Criterion Details

Exclusion Criterion #7: Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization.

Note: for a potential participant who regularly receives chronic supplementary oxygen for an underlying lung condition, oxygen saturation should be measured while on their standard home oxygen supplementation.

10.9.7. Prior/Concomitant Therapy

Exclusion Criterion #9: Current use of any prohibited concomitant medication(s).

1. Current use of any medications that are highly dependent on CYP3A4 for clearance and which are contraindicated in combination with nirmatrelvir/ritonavir (see Appendix 8). Participants taking lovastatin and simvastatin may enroll, provided that they have discontinued use at least 12h prior to initiation of nirmatrelvir/ritonavir and refrain from use during treatment and for 5 days after the last dose of study intervention. Coadministration of nirmatrelvir/ritonavir with other medications that are not contraindicated but are highly dependent on CYP3A4 for clearance may require dose adjustment or additional monitoring (See Appendix 8 in protocol).

2. Use of any medications or substances that are strong inducers of CYP3A4 and that are contraindicated in combination with nirmatrelvir/ritonavir without the appropriate washout prior to the first dose of nirmatrelvir/ritonavir (see Appendix 8 in protocol). The appropriate washout period for CYP3A4 inducers should be determined based on the prescribing information for the concomitant medication and in consultation with the medical monitor.

3. Use of an antiviral or monoclonal antibody therapy for the treatment of COVID-19 within 30 days prior to screening, except for participants in the additional population with rebound, who must have completed a recent (ie, within 14 days) initial 5-day course of nirmatrelvir/ritonavir (see Section 10.9.5).

4. Current or expected use of a non-study antiviral or monoclonal antibody therapy for the treatment of COVID-19 within 15 days after randomization.

10.10. Appendix 10: Participant-Reported COVID-19-Related Signs and Symptoms

Sign and Symptom Collection[4]	Entry Criterion #3 Targeted (used for study entry)	Signs and Symptom Collection
Cough	X	X
Shortness of breath or difficulty breathing	X	X
Fever (documented temperature >38˚C [100.4˚F]) or subjective fever (eg, feeling feverish)	X	
Feeling feverish		X
Chills or shivering	X	X
Fatigue (low energy or tiredness)	X	X
Muscle or body aches	X	X
Diarrhea (loose or watery stools)	X	X
Nausea (feeling like you wanted to throw up)	X	X
Vomiting (throw up)	X	X
Headache	X	X
Sore throat	X	X
Stuffy or runny nose	X	X
Loss of smell	X	X
Loss of taste	X	X

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
AAP	American Academy of Pediatrics
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BID	twice a day
BP	blood pressure
CAR-T	chimeric antigen receptor T-cell
CDC	United States Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
CT	computed tomography/clinical trial
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DAIDS	Division of AIDS
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
EC	ethics committee
ECC	emergency contact card
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram or electrocardiography
ECMO	extracorporeal membrane oxygenation
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee

Abbreviation	Term
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-3L	Euroquol Quality of Life 5 Dimension 3-Level Scale
EPIC-HR	Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients
ePRO	electronic patient-reported outcome
EQ-5D-5L	Euroquol Quality of Life 5
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EUA	Emergency Use Authorization
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
H	home
HCP	healthcare professional
HCT	hematopoietic cell transplantation
HCV	hepatitis C virus
HDPE	high density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl co-enzyme A
HRT	hormone replacement therapy
HTA	health technology assessment
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRT	Interactive Response Technology

Abbreviation	Term
JAK	Janus Kinase
KDIGO	Kidney Disease: Improving Global Outcomes
LFT	liver function test
LLOQ	lower limit of quantitation
LT	long-term
mAb	monoclonal antibody
MIS-C	multisystem inflammatory syndrome in children
MQI	medically qualified individual
n	number
NA	not applicable
NCT	National Clinical Trial
NIH	National Institutes of Health
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
NP	nasopharyngeal
P	participant's location
PACL	protocol administrative change letter
PDE5	phosphodiesterase-5
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
POC	point-of-care
PR	pulse rate
PRO	patient-reported outcome
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
q12h	every 12 hours
QTL	quality tolerance limit
RBC	red blood cell
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
S	investigational site
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SF-36	Short Form-36
sGC	soluble guanylate cyclase
SoA	schedule of activities
SoC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Term
T4	thyroxine
T bili	total bilirubin
TEAE	treatment-emergent adverse event(s)
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WONCBP	woman/women not of childbearing potential
WPAI	Work Productivity and Activity Impairment
WPAI-GH	Work Productivity and Activity Impairment – General Health

11. REFERENCES

1. Abbasi J. Researchers Tie Severe Immunosuppression to Chronic COVID-19 and Virus Variants. JAMA. 2021;325(20):2033-35.
2. Corey L, Beyrer C, Cohen MS, et al. SARS-CoV-2 Variants in Patients with Immunosuppression. N Engl J Med. 2021;385(6):562-66.
3. World Health Organization. (2022). WHO Situation Report - 51 Coronavirus disease 2019 (COVID-19). 11 March 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed on: 26 May 2022.
4. US Food and Drug Administration. Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment. September 2020 2020. Available from: https://www.fda.gov/media/142143/download. Accessed on: 18 May 2022.
5. US Food and Drug Administration. COVID-19 Vaccines. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines. Accessed on: 29 Jun 2021.
6. Parker EPK, Desai S, Marti M, et al. Response to additional COVID-19 vaccine doses in people who are immunocompromised: a rapid review. Lancet Glob Health. 2022;10(3):e326-e28.
7. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England. 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042367/technical_briefing-31-10-december-2021.pdf. Accessed on: 02 March 2022.
8. Centers for Disease Control and Prevention. COVID Data Tracker. Variant Proportions. Available from: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed on: 23 March 2022.
9. National Institutes of Health. Characteristics of SARS-CoV-2 Antibody-Based Products. Report Number: 08 April 2022. Available from: https://www.covid19treatmentguidelines.nih.gov/tables/mab-characteristics/. Accessed on: 26 April 2022.
10. Infectious Disease Society of America. FDA EUA for COVID-19 pre-exposure prophylaxis with long-acting monoclonals is a key proof of concept. 2021. Available from: https://www.idsociety.org/science-speaks-blog/2021/fda-eua-for-covid-19-pre-exposure-prophylaxis-with-long-acting-monoclonals-is-a-key-proof-of-concept/. Accessed on: 22 February 2022.
11. US Food and Drug Administration. Fact sheet for healthcare providers emergency use authorization of Paxlovid™. Available from: https://www.fda.gov/media/155050/download. Accessed on: 27 July 2022.
12. US Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Molnupiravir. February 2022. Available from: https://www.fda.gov/media/155054/download. Accessed on: 22 February 2022.
13. Veklury (remdesivir). US Prescribing Information (USPI); April 2022, Foster City, CA, USA: Gliead Sciences, Inc. Available from: https://www.gilead.com/-

/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf. Accessed on: 26 May 2022.
14. Carlin AF, Clark AE, Chaillon A, et al. Virologic and Immunologic Characterization of COVID-19 Recrudescence after Nirmatrelvir/Ritonavir Treatment. Preprint: 18 May 2022. Clin Infect Dis. 2022;10.1093/cid/ciac496.
15. Gupta K. SJ, Stack G., et al. Rapid Relapse of Symptomatic SARS-CoV-2 Infection Following Early Suppression with Nirmatrelvir/Ritonavir. Preprint 26 Apr 2022. Report Number: v1. 2022. Available from: https://doi.org/10.21203/rs.3.rs-1588371/v1.
16. Charness M GK, Stack G, et al. (2022). Rapid Relapse of Symptomatic Omicron SARS-CoV-2 Infection Following Early Suppression with Nirmatrelvir/Ritonavir. Preprint: 23 May Available from: https://www.researchsquare.com/article/rs-1588371/v3.
17. Ranganath N, O'Horo JC, Challener DW, et al. Rebound Phenomenon after Nirmatrelvir/Ritonavir Treatment of Coronavirus Disease-2019 in High-Risk Persons. Clin Infect Dis. 2022;10.1093/cid/ciac481.
18. Docherty AB, Harrison EM, Green CA, et al. Features of 20,133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985.
19. Centers for Disease Control and Prevention. People With Certain Medical Conditions. Updated 02 May 2022. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.
20. Nichols WG, Guthrie KA, Corey L, et al. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis. 2004;39(9):1300-6.
21. Boivin G, Goyette N, Bernatchez H. Prolonged excretion of amantadine-resistant influenza a virus quasi species after cessation of antiviral therapy in an immunocompromised patient. Clin Infect Dis. 2002;34(5):E23-5.
22. Kemp SA, Collier DA, Datir RP, et al. SARS-CoV-2 evolution during treatment of chronic infection. Nature. 2021;592(7853):277-82.
23. Gandhi S, Klein J, Robertson AJ, et al. De novo emergence of a remdesivir resistance mutation during treatment of persistent SARS-CoV-2 infection in an immunocompromised patient: a case report. Nat Commun. 2022;13(1):1547.
24. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022;386(15):1397-408.
25. Pfizer. Investigator's Brochure PF-07321332. Data on file.
26. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP), CHMP assessment report, Paxlovid. Report Number: 16 December 2021. Available from: {European Medicines Agency, #190}. Accessed on: 08 March 2022.
27. Dai W, Rao R, Sher A, et al. A Prototype QSP Model of the Immune Response to SARS-CoV-2 for Community Development. CPT Pharmacometrics Syst Pharmacol. 2021;10(1):18-29.
28. Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19. Science. 2021;374(6575):1586-93.

29. Pfizer Inc. Study C4671011. A Phase 1, Non-Randomized, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of PF-07321332 Boosted With Ritonavir in Adult Participants With Renal Impairment and in Healthy Participants With Normal Renal Function. Clinical Study Report. 19 November 2021.
30. CDC. COVID-19. May 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2Findex.html. Accessed on: 23 May 2022.
31. US Food and Drug Administration. Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment. 2020. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-covid-19-related-symptoms-outpatient-adult-and-adolescent-subjects-clinical-trials-drugs. Accessed on: 25 Mar 2021.
32. US Bureau of Labor Statistics. (2021). Effects of COVID-19 Pandemic on Productivity and Costs Statistics Updated 18 November 2021. Available from: https://www.bls.gov/covid19/effects-of-covid-19-pandemic-on-productivity-and-costs-statistics.htm. Accessed on: 26 May 2022.
33. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353-65.
34. Rabin R, Gudex C, Selai C, et al. From translation to version management: a history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. Value Health. 2014;17(1):70-6.
35. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.
36. Ramos-Goni JM, Pinto-Prades JL, Oppe M, et al. Valuation and Modeling of EQ-5D-5L Health States Using a Hybrid Approach. Med Care. 2017;55(7):e51-e58.
37. Yang Y, Brazier J, Longworth L. EQ-5D in skin conditions: an assessment of validity and responsiveness. Eur J Health Econ. 2015;16(9):927-39.
38. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-27.
39. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
40. Agborsangaya CB, Lahtinen M, Cooke T, et al. Comparing the EQ-5D 3L and 5L: measurement properties and association with chronic conditions and multimorbidity in the general population. Health Qual Life Outcomes. 2014;12:74.
41. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
42. U.S. Department of Health and Human Services NIoH, National Heart, Lung, and Blood Institute. A Pocket Guide to Blood Pressure Measurement in Children. May 2007. Available from: https://www.nhlbi.nih.gov/files/docs/bp_child_pocket.pdf. Accessed on: 16 February 2022.
43. U.S. Department of Health and Human Services NIoH, National Institute of Allergy and Infectious Diseases, Division of AIDS,. Division of AIDS (DAIDS) Table for

Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. July 2017. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Accessed on: 10 Jun 2021.

44. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737-49.