



## Title Page

**A PHASE 1, OPEN-LABEL, RANDOMIZED, SINGLE DOSE, CROSSOVER STUDY  
TO ESTIMATE THE RELATIVE BIOAVAILABILITY OF NIRMATRELVIR  
(PF-07321332) /RITONAVIR ORAL POWDER IN 3 DIFFERENT FOOD DELIVERY  
VEHICLES RELATIVE TO THE NIRMATRELVIR (PF-07321332) /RITONAVIR  
COMMERCIAL TABLETS UNDER FASTED CONDITIONS, AND THE EFFECT  
OF FOOD ON RELATIVE BIOAVAILABILITY OF NIRMATRELVIR  
(PF-07321332) /RITONAVIR ORAL POWDER IN HEALTHY ADULT  
PARTICIPANTS**

**Study Intervention Number:** Nirmatrelvir (PF-07321332)

**Study Intervention Name:** NA

**US IND Number:** 153517

**EudraCT Number:** 2022-002497-86

**ClinicalTrials.gov ID:** NA

**Pediatric Investigational Plan Number:** NA

**Protocol Number:** C4671036

**Phase:** 1

**Brief Title:** A Phase 1 Relative Bioavailability Study of Nirmatrelvir/Ritonavir Oral Powder Relative to the Nirmatrelvir/Ritonavir Commercial Tablets, and Estimation of the Effect of Food on Bioavailability of the Nirmatrelvir/Ritonavir Oral Powder in Healthy Participants

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

### Document History

Document	Version Date
Original protocol	19 July 2022

## TABLE OF CONTENTS

LIST OF TABLES .....	8
1. PROTOCOL SUMMARY .....	9
1.1. Synopsis .....	9
1.2. Schema .....	15
1.3. Schedule of Activities .....	16
2. INTRODUCTION .....	21
2.1. Study Rationale .....	21
2.2. Background .....	21
2.2.1. Nonclinical Pharmacology.....	21
2.2.2. Nonclinical Pharmacokinetics and Metabolism .....	21
2.2.3. Nonclinical Safety .....	22
2.2.4. Clinical Overview .....	22
2.2.4.1. Safety Overview .....	23
2.2.4.2. Summary of Nirmatrelvir Pharmacokinetics in Human.....	24
2.3. Benefit/Risk Assessment.....	26
2.3.1. Risk Assessment .....	27
3. OBJECTIVES AND ENDPOINTS .....	29
4. STUDY DESIGN.....	30
4.1. Overall Design.....	30
4.2. Scientific Rationale for Study Design .....	32
4.2.1. Choice of Contraception/Barrier Requirements .....	32
4.2.2. Collection of Retained Research Samples .....	32
4.3. Justification for Dose .....	33
4.4. End of Study Definition .....	33
5. STUDY POPULATION .....	33
5.1. Inclusion Criteria.....	33
5.2. Exclusion Criteria.....	34
5.3. Lifestyle Considerations.....	37
5.3.1. Contraception.....	37
5.3.2. Meals and Dietary Restrictions.....	37
5.3.3. Caffeine, Alcohol, and Tobacco .....	38

5.3.4. Activity .....	38
5.4. Screen Failures .....	38
6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY .....	39
6.1. Study Intervention(s) Administered .....	39
6.1.1. Administration .....	40
6.2. Preparation, Handling, Storage, and Accountability .....	41
6.2.1. Preparation and Dispensing .....	42
6.3. Assignment to Study Intervention .....	43
6.4. Blinding .....	43
6.5. Study Intervention Compliance .....	43
6.6. Dose Modification .....	43
6.7. Continued Access to Study Intervention After the End of the Study .....	43
6.8. Treatment of Overdose .....	43
6.9. Prior and Concomitant Therapy .....	44
6.9.1. Rescue Medicine .....	44
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL .....	45
7.1. Discontinuation of Study Intervention .....	45
7.1.1. ECG Changes .....	45
7.1.2. Potential Cases of Acute Kidney Injury .....	45
7.1.3. Stopping Rules .....	46
7.2. Participant Discontinuation/Withdrawal From the Study .....	46
7.2.1. Withdrawal of Consent .....	47
7.3. Lost to Follow-up .....	47
8. STUDY ASSESSMENTS AND PROCEDURES .....	48
8.1. Administrative Procedures .....	48
8.2. Efficacy Assessments .....	49
8.3. Safety Assessments .....	49
8.3.1. Physical Examinations .....	49
8.3.2. Vital Signs .....	50
8.3.2.1. Blood Pressure and Pulse Rate .....	50
8.3.3. Electrocardiograms .....	50

8.3.4. Clinical Safety Laboratory Assessments .....	51
8.3.5. COVID-19 Specific Assessments .....	51
8.3.6. Pregnancy Testing .....	52
8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting .....	52
8.4.1. Time Period and Frequency for Collecting AE and SAE Information.....	52
8.4.1.1. Reporting SAEs to Pfizer Safety .....	53
8.4.1.2. Recording Nonserious AEs and SAEs on the CRF .....	53
8.4.2. Method of Detecting AEs and SAEs .....	54
8.4.3. Follow-Up of AEs and SAEs.....	54
8.4.4. Regulatory Reporting Requirements for SAEs.....	54
8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure .....	54
8.4.5.1. Exposure During Pregnancy.....	55
8.4.5.2. Exposure During Breastfeeding .....	56
8.4.5.3. Occupational Exposure .....	57
8.4.6. Cardiovascular and Death Events .....	57
8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs.....	57
8.4.8. Adverse Events of Special Interest .....	57
8.4.8.1. Lack of Efficacy .....	57
8.4.9. Medical Device Deficiencies .....	57
8.4.9.1. Time Period for Detecting Medical Device Deficiencies .....	57
8.4.9.2. Follow-Up of Medical Device Deficiencies.....	57
8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor .....	58
8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies .....	58
8.4.10. Medication Errors .....	58
8.5. Pharmacokinetics .....	59
8.5.1. Plasma for Analysis of Nirmatrelvir and Ritonavir .....	59
8.6. Genetics .....	60
8.6.1. Specified Genetics .....	60
8.6.2. Retained Research Samples for Genetics .....	60

CCI

PFIZER CONFIDENTIAL

8.7.1. Specified Gene Expression (RNA) Research .....	60
8.7.2. Specified Protein Research .....	60
8.7.3. Specified Metabolomic Research .....	60
CCI .....	
8.8. Immunogenicity Assessments .....	61
8.9. Health Economics .....	61
8.10. Taste Assessment of Nirmatrelvir Oral Powder .....	61
9. STATISTICAL CONSIDERATIONS .....	61
9.1. Statistical Hypotheses .....	61
9.2. Analysis Sets .....	61
9.3. Statistical Analyses .....	62
9.3.1. Pharmacokinetic Analyses .....	62
9.3.1.1. Derivation of Pharmacokinetic Parameters .....	62
9.3.2. Statistical Methods for PK Data .....	63
9.3.3. Other Safety Analyses .....	63
9.3.4. Other Analyse(s) .....	64
9.3.4.1. Taste Assessment .....	64
9.3.4.2. Biomarker Assessment .....	64
9.4. Interim Analyses .....	64
9.5. Sample Size Determination .....	64
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS .....	66
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations .....	66
10.1.1. Regulatory and Ethical Considerations .....	66
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP .....	66
10.1.2. Financial Disclosure .....	67
10.1.3. Informed Consent Process .....	67
10.1.4. Data Protection .....	68
10.1.5. Committees Structure .....	68
10.1.5.1. Data Monitoring Committee .....	68
10.1.6. Dissemination of Clinical Study Data .....	68
10.1.7. Data Quality Assurance .....	69

10.1.8. Source Documents .....	71
10.1.9. Study and Site Start and Closure .....	71
10.1.10. Publication Policy .....	72
10.1.11. Sponsor's Medically Qualified Individual.....	73
10.2. Appendix 2: Clinical Laboratory Tests .....	74
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting .....	75
10.3.1. Definition of AE .....	75
10.3.2. Definition of an SAE .....	76
10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period.....	77
10.3.4. Reporting of SAEs.....	81
10.4. Appendix 4: Contraceptive and Barrier Guidance .....	82
10.4.1. Male Participant Reproductive Inclusion Criteria .....	82
10.4.2. Female Participant Reproductive Inclusion Criteria.....	82
10.4.3. Woman of Childbearing Potential .....	82
10.4.4. Contraception Methods.....	83
10.5. Appendix 5: Genetics .....	85
10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments .....	86
10.7. Appendix 7: Kidney Safety: Monitoring Guidelines .....	88
10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury .....	88
10.7.2. Age-Specific Kidney Function Calculation Recommendations .....	88
10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations .....	88
10.7.2.2. Adolescents (12 Years to <18 Years)—Cockcroft-Gault Formula.....	89
10.7.2.3. Children (2 Years to <12 Years)—Modified Schwartz Equation.....	89
10.7.2.4. Infants (1 Month to <2 Years) and Neonates (<1 Month)—Bedside Schwartz Equation.....	89
10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities.....	89
10.8. Appendix 8: ECG Findings of Potential Clinical Concern .....	90

10.9. Appendix 9: Palatability Questionnaire .....92

10.10. Appendix 10: Abbreviations .....100

11. REFERENCES .....104

**LIST OF TABLES**

Table 1. Study Schedule of Assessment .....16

Table 2. Pharmacokinetic Sampling Schema .....20

Table 3. Randomized Treatment Sequences.....31

Table 4. Plasma Nirmatrelvir and Ritonavir PK Parameters Definitions .....62

Table 5. Protocol-Required Safety Laboratory Assessments .....74

## 1. PROTOCOL SUMMARY

### 1.1. Synopsis

**Protocol Title:** A Phase 1, Open-Label, Randomized, Single Dose, Crossover Study to Estimate the Relative Bioavailability of Nirmatrelvir (PF-07321332)/Ritonavir Oral Powder in 3 Different Food Delivery Vehicles Relative to the Nirmatrelvir/Ritonavir Commercial Tablets Under Fasted Conditions and the Effect of Food on Relative Bioavailability of Nirmatrelvir (PF-07321332) /Ritonavir Oral Powder in Healthy Adult Participants

**Brief Title:** A Phase 1 Relative Bioavailability Study of Nirmatrelvir/Ritonavir Oral Powder Relative to the Nirmatrelvir/Ritonavir Commercial Tablets, and Estimation of the Effect of Food on Bioavailability of the Nirmatrelvir/Ritonavir Oral Powder in Healthy Participants.

### Regulatory Agency Identification Number(s):

US IND Number:	153517
EudraCT Number:	2022-002497-86
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4671036
Phase:	1

### Rationale:

Nirmatrelvir, a potent and selective inhibitor of the SARS-CoV-2 M<sup>pro</sup> is being developed as an oral treatment for COVID-19. Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of nirmatrelvir in order to increase plasma concentrations of nirmatrelvir sufficient to suppress viral replication through the entire dosing interval. The clinical development program for nirmatrelvir includes 12 completed clinical studies: 8 Phase 1 studies in healthy participants (C4671001, C4671008, C4671019, C4671024, C4671012, C4671013, C4671014 and C4671015), 1 Phase 1 study in renal impairment participants (C4671011), 1 Phase 1 study in hepatic impaired participants (C4671010) and 2 Phase 2/3 pivotal studies in COVID-19 patients (C4671005 and C4671006).

The purpose of this study is to estimate the rBA of nirmatrelvir/ritonavir oral powder in 3 different food vehicles relative to the Paxlovid<sup>®</sup> tablets under fasted condition in healthy adult participants, and to estimate the effect of food on the rBA of the nirmatrelvir/ritonavir oral powder formulation. The study will also assess the safety, tolerability, and palatability of nirmatrelvir/ritonavir oral powder in healthy adult participants.

## Objectives and Endpoints:

Objectives	Endpoints
<b>Primary:</b>	<b>Primary:</b>
<ul style="list-style-type: none"> <li>To estimate the rBA of the nirmatrelvir/ritonavir CCI oral powder mixed with water compared to the nirmatrelvir/ritonavir CCI commercial tablets under fasted conditions.</li> <li>To estimate the rBA of the nirmatrelvir/ritonavir CCI oral powder mixed with infant formula compared to the nirmatrelvir/ritonavir CCI commercial tablets under fasted conditions.</li> <li>To estimate the rBA of the nirmatrelvir/ritonavir CCI oral powder mixed with vanilla pudding compared to the nirmatrelvir/ritonavir CCI commercial tablets under fasted conditions.</li> <li>To estimate the rBA of the nirmatrelvir/ritonavir CCI oral powder mixed with vanilla pudding under fed conditions compared to the nirmatrelvir/ritonavir CCI commercial tablets under fasted conditions.</li> </ul>	<ul style="list-style-type: none"> <li>The test/reference ratios for <math>AUC_{inf}</math> (if data permits), <math>AUC_{last}</math>, and <math>C_{max}</math> of nirmatrelvir and ritonavir.</li> </ul>
<b>Secondary:</b>	<b>Secondary:</b>
<ul style="list-style-type: none"> <li>To estimate the effect of food on the rBA of the nirmatrelvir/ritonavir CCI oral powder mixed with vanilla pudding.</li> <li>To evaluate the safety and tolerability of nirmatrelvir/ritonavir in healthy participants.</li> <li>To assess the palatability of nirmatrelvir/ritonavir oral powder mixed with water/ infant formula/ vanilla pudding.</li> </ul>	<ul style="list-style-type: none"> <li>The test/reference ratios for <math>AUC_{inf}</math> (if data permits), <math>AUC_{last}</math>, and <math>C_{max}</math> of nirmatrelvir and ritonavir.</li> <li>Assessment of TEAEs, clinical laboratory abnormalities, vital signs, PEs, and 12 lead ECGs.</li> <li>Assessment of palatability via questionnaire: mouth feel, bitterness, tongue/mouth burn, throat burn and overall liking.</li> </ul>

Objectives	Endpoints
CCI [REDACTED]	[REDACTED]
I [REDACTED]	I [REDACTED]
I [REDACTED]	I [REDACTED]

### Overall Design:

This is a Phase 1, open-label, single dose, randomized, crossover study in healthy adult participants to estimate rBA of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with 3 different delivery vehicles (Test formulations) compared to the nirmatrelvir/ritonavir CCI [REDACTED] commercial tablets (Reference formulation) under fasted conditions, and to estimate the effect of food on the rBA of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with vanilla pudding. The study will also assess the safety, tolerability, and palatability of nirmatrelvir/ritonavir oral powder in healthy adult participants.

The study will consist of 5 treatments:

- A single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] tablets under fasted condition (Treatment A)
- A single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in water under fasted condition (Treatment B)
- A single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in infant formula under fasted condition (Treatment C)
- A single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in vanilla pudding under fasted condition (Treatment D)
- A single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in vanilla pudding under fed condition (Treatment E)

Between each treatment, a minimum of 4 days washout is required to minimize any residual nirmatrelvir and ritonavir concentrations prior to start of the next treatment.

Approximately 12 healthy adult male and/or female participants will be randomized to the study. Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the investigator.

Healthy participants will be screened to determine eligibility within 28 days prior to study treatment. Medical history and results of PE, vital signs, 12-lead ECG, and clinical laboratory evaluations will determine eligibility. Eligible participants will be admitted to the CRU on Period 1 Day -1 and will be confined in the CRU until discharge which is Day 4 of Period 5.

On Day 1 of each period, participants will receive a single oral dose of study interventions nirmatrelvir/ritonavir CCI [REDACTED] as per the randomization schedule.

Study treatments A, and D will be administered with approximately 240 mL of ambient temperature water and study treatments B and C will be administered with approximately 210 mL of ambient temperature water under fasted conditions (10 hours overnight fast and no food until 4 hours after dosing). Study treatments E will be administered with approximately 240 mL of ambient temperature water approximately 30 minutes after the start of a standard high-fat, high-calorie breakfast. Serial PK samples will be collected up to 72 hours post dose. Participants will be discharged from the CRU on Period 5, Day 4 following completion of all assessments.

If a participant has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

A safety follow-up call will be made to participants approximately 28 to 35 days from administration of the final dose of study intervention.

### **Number of Participants:**

Approximately 12 participants will be randomly assigned to study intervention such that approximately 2 participants will be enrolled into 1 of 6 sequences.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent 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, unless otherwise specified by the protocol.

## 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. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, PE, laboratory tests, vital signs and standard 12-lead ECG.

### Exclusion Criteria

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

1. Positive test result for SARS-CoV-2 infection on Day -1.
2. Participants who have received a COVID-19 vaccine within 7 days before screening or admission, or who are to be vaccinated with a COVID-19 vaccine at any time during the study confinement period.

## Study Arms and Duration:

Each enrolled participant will participate in 5 study periods to receive 5 different treatments according to the sequence determined by randomization:

- Treatment A: Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] tablets under fasted condition
- Treatment B: Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in water under fasted condition
- Treatment C: Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in infant formula under fasted condition
- Treatment D: Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in vanilla pudding under fasted condition
- Treatment E: Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in vanilla pudding under fed condition

Participants will be randomly assigned to 1 of 6 sequences as below:

Treatment Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
Sequence 1 (N = 2)	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E
Sequence 2 (N = 2)	Treatment B	Treatment C	Treatment A	Treatment D	Treatment E
Sequence 3 (N = 2)	Treatment C	Treatment A	Treatment B	Treatment D	Treatment E
Sequence 4 (N = 2)	Treatment A	Treatment C	Treatment B	Treatment E	Treatment D
Sequence 5 (N = 2)	Treatment B	Treatment A	Treatment C	Treatment E	Treatment D
Sequence 6 (N = 2)	Treatment C	Treatment B	Treatment A	Treatment E	Treatment D

Between each treatment, a minimum of 4 days washout is proposed to minimize any residual nirmatrelvir and ritonavir concentrations prior to start of the next treatment. Participants will be discharged on Day 4 of Period 5, following completion of all assessments.

The total planned duration of participation from the Screening visit to the last follow-up phone call, is approximately 12 weeks.

Study Intervention(s)				
Intervention Name	Nirmatrelvir Tablets	Ritonavir Tablets	Nirmatrelvir Oral Powder	Ritonavir Oral Powder
Arm Name (group of participants receiving a specific treatment or no treatment)	nirmatrelvir/ritonavir commercial tablets	nirmatrelvir/ritonavir commercial tablets	nirmatrelvir/ritonavir oral powder	nirmatrelvir/ritonavir oral powder
Unit Dose Strength(s)	CCI			
Route of Administration	Oral	Oral	Oral	Oral
IMP or NIMP/AxMP	IMP	NIMP	IMP	IMP
Former name	PF-07321332		PF-07321332	

Study Arm(s)					
Arm Title	Nirmatrelvir/ritonavir commercial tablets	Nirmatrelvir/ritonavir oral powder mixed with water	Nirmatrelvir/ritonavir oral powder mixed with infant formula	Nirmatrelvir/ritonavir oral powder mixed with vanilla pudding (fasted)	Nirmatrelvir/ritonavir oral powder mixed with vanilla pudding (fed)
Arm Type	Reference	Experimental	Experimental	Experimental	Experimental

Study Arm(s)					
Arm Description	Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] commercial tablets under fasted conditions	Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with water under fasted conditions	Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with infant formula under fasted conditions	Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with vanilla pudding under fasted conditions	Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with vanilla pudding under fed conditions

## Statistical Methods:

Natural log transformed  $AUC_{inf}$  (if data permits),  $AUC_{last}$  and  $C_{max}$  will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within a sequence as a random effect.

## Ethical Considerations:

Nirmatrelvir is not expected to provide any clinical benefit to healthy participants in this study. This study is designed primarily to further the understanding of human PK of nirmatrelvir.

Based on data from Study C4671001, C4671019, C4671024, C4671005 and C4671006, the clinical safety profile of nirmatrelvir appears to be acceptable at single doses up to 1500 mg alone and up to 2250 mg administered with ritonavir (100 mg at -12h, 0h, 12h), split dosing administration (3 doses of 750 mg) at short intervals (approximately 2 hours from the previous dose), and at repeated daily doses administered orally for 10 days of up to 500 mg nirmatrelvir q12h with 100 mg ritonavir q12h.

## 1.2. Schema

Not Applicable.

### 1.3. Schedule of Activities

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

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

**Table 1. Study Schedule of Assessment**

Visit Identifier Abbreviations used in this table may be found in <a href="#">Appendix 10</a>	Screening	Period 1					Period 2, 3 and 4				Period 5				F/U	E/T	Notes
Days Relative to Day 1	Days -28 to -2	Day -1	1	2	3	4	1	2	3	4	1	2	3	4	28-35 Days		<ul style="list-style-type: none"><li>Screening will be performed within 28 days prior to the first dose of nirmatrelvir/ritonavir.</li><li>Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.</li></ul>
Informed consent	X																<ul style="list-style-type: none"><li>Informed consent should be obtained prior to undergoing any study-specific procedures</li></ul>
CRU Confinement		X	→	→	→	→	→	→	→	→	→	→	→	X		X	<ul style="list-style-type: none"><li>Participants will be admitted to the CRU on Period 1 Day -1. Participants will be discharged on Period 5 Day 4 following the final assessments.</li></ul>
Inclusion/ exclusion criteria	X	X															<ul style="list-style-type: none"><li>See Sections <a href="#">5.1</a> and <a href="#">5.2</a> for additional information.</li></ul>
Medical/ medication history (update)	X	X															<ul style="list-style-type: none"><li>Medical history will include a history of prior illegal drug, alcohol, and tobacco use, as well as blood donation within prior 60 days. Medical history will be recorded at Screening and updated on Period 1 Day -1.</li></ul>
Demography	X																<ul style="list-style-type: none"><li>Demographics will include participant race, ethnicity, age, and gender during the Screening visit.</li></ul>

**Table 1. Study Schedule of Assessment**

Visit Identifier Abbreviations used in this table may be found in <a href="#">Appendix 10</a>	Screening	Period 1					Period 2, 3 and 4				Period 5				F/U	E/T	Notes
Days Relative to Day 1	Days -28 to -2	Day -1	1	2	3	4	1	2	3	4	1	2	3	4	28-35 Days		
Physical Exam	X	X															<ul style="list-style-type: none"> <li>Screening will be performed within 28 days prior to the first dose of nirmatrelvir/ritonavir.</li> <li>Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.</li> </ul>
Safety laboratory	X	X												X		X	<ul style="list-style-type: none"> <li>Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed at Screening, Period 1 Day -1, Period 5 Day 4, and early termination/discontinuation if applicable. All the safety laboratory samples must be collected following at least a 4-hour fast. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator.</li> </ul>
FSH (postmenopausal women only)	X																<ul style="list-style-type: none"> <li>For confirmation of postmenopausal (amenorrheic for at least 12 consecutive months) female participants.</li> </ul>
Urine drug testing	X	X															<ul style="list-style-type: none"> <li>Urine drug (mandatory) and alcohol breath test (at discretion of investigator) will be performed at Screening and on Period 1 Day -1. These tests may be performed at any other time at the discretion of the investigator.</li> </ul>
Serology: HBsAg, HBsAb, HBcAb, HCVAb, and HIV	X																<ul style="list-style-type: none"> <li>HBsAb will be tested if HBsAg and/or HBcAb are positive.</li> </ul>
Pregnancy test (WOCBP only)	X	X												X		X	

**Table 1. Study Schedule of Assessment**

Visit Identifier Abbreviations used in this table may be found in <a href="#">Appendix 10</a>	Screening	Period 1					Period 2, 3 and 4				Period 5				F/U	E/T	Notes
Days Relative to Day 1	Days -28 to -2	Day -1	1	2	3	4	1	2	3	4	1	2	3	4	28-35 Days		<ul style="list-style-type: none"> <li>Screening will be performed within 28 days prior to the first dose of nirmatrelvir/ritonavir.</li> <li>Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.</li> </ul>
Contraception check	X	X												X	X	X	<ul style="list-style-type: none"> <li>The investigator or his/her designee will discuss with the participant the need to use highly effective contraception consistently and correctly according to contraception guidelines (<a href="#">Appendix 4</a>).</li> </ul>
12-lead ECG (single)	X		X											X		X	<ul style="list-style-type: none"> <li>Single 12-lead ECG readings will be taken at specified time point. All ECG assessments will be made after at least a 5-minute rest in a supine position and prior to any blood draws or vital sign measurements.</li> <li>The reading on Period 1 Day 1 will be done predose of Period 1 Day 1.</li> </ul>
Vital signs (BP/PR)	X		X				X				X			X		X	<ul style="list-style-type: none"> <li>Single supine BP and PR will be performed following at least a 5-minute rest in a supine position, at specified time point. BP, and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time. Vital signs will be done predose, 2 hours and 6 hours post dose on Day 1 of each treatment period and also on Day 4 of Period 5.</li> </ul>
COVID-19 questionnaire		X															<ul style="list-style-type: none"> <li>Check COVID-19 related signs and symptoms as per local procedures.</li> </ul>
COVID-19 testing		X				X											<ul style="list-style-type: none"> <li>The testing for COVID-19 pathogen by RT-PCR will be performed as per local procedures.</li> </ul>
Nirmatrelvir/ ritonavir dosing			X				X				X						<ul style="list-style-type: none"> <li>Nirmatrelvir/ritonavir will be administered orally after overnight fasting of 10 hours on Day 1 for treatments A, B, C and D and after high fat breakfast for treatment E. There will be at least a 4 day washout between each dose.</li> </ul>

**Table 1. Study Schedule of Assessment**

Visit Identifier Abbreviations used in this table may be found in <a href="#">Appendix 10</a>	Screening	Period 1				Period 2, 3 and 4				Period 5				F/U	E/T	Notes	
Days Relative to Day 1	Days -28 to -2	Day -1	1	2	3	4	1	2	3	4	1	2	3	4	28-35 Days		<ul style="list-style-type: none"><li>Screening will be performed within 28 days prior to the first dose of nirmatrelvir/ritonavir.</li><li>Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.</li></ul>
Palatability questionnaire Review			X				X										<ul style="list-style-type: none"><li>Review palatability questionnaire and instructions with participants prior to the first taste assessment to Treatment B, C and D on Day 1 of period 1 or 2.</li></ul>
Palatability Questionnaire			X				X				X						<ul style="list-style-type: none"><li>Each participant will record the sensory attributes at timed intervals of 1 (immediately after dosing), 5, 10 and 20 minutes after swallowing the suspension, using a Taste Assessment Questionnaire (see <a href="#">Appendix 9</a>).</li><li>PK assessments will take priority if the PK and palatability assessment conflict</li></ul>
PK Blood Sampling for nirmatrelvir/ ritonavir			X	X	X	X	X	X	X	X	X	X	X	X		X	<ul style="list-style-type: none"><li>One (approximately 4 mL) blood sample for PK analysis of nirmatrelvir and ritonavir will be taken at the designated time points. See PK sampling schema in <a href="#">Table 2</a>.</li></ul>
CCI																	
CCI																	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	<ul style="list-style-type: none"><li>See Section <a href="#">8.4.3</a> for follow-up AE and SAE assessments.</li></ul>
Concomitant treatments	X	X	X	→	→	→	→	→	→	→	→	→	→	X	X	X	<ul style="list-style-type: none"><li>See Section <a href="#">6.9</a> for additional information.</li></ul>

PFIZER CONFIDENTIAL

**Table 1. Study Schedule of Assessment**

Visit Identifier Abbreviations used in this table may be found in <a href="#">Appendix 10</a>	Screening	Period 1					Period 2, 3 and 4				Period 5				F/U	E/T	Notes
Days Relative to Day 1	Days -28 to -2	Day -1	1	2	3	4	1	2	3	4	1	2	3	4	28-35 Days		<ul style="list-style-type: none"><li>Screening will be performed within 28 days prior to the first dose of nirmatrelvir/ritonavir.</li><li>Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.</li></ul>
CRU discharge														X			<ul style="list-style-type: none"><li>Participants will be discharged from clinic on Day 4 of period 5 after collection of last PK sample.</li></ul>

**Table 2. Pharmacokinetic Sampling Schema**

Visit Identifier	Treatment Period 1 to 5														
Study Day	Day 1												Day 2	Day 3	Day 4
Planned Hours Post Dose on That Day	0	0.5	1	1.5	2	2.5	3	4	6	8	12	16	24	48	72
PK blood sampling for nirmatrelvir/ritonavir	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

## 2. INTRODUCTION

Nirmatrelvir a potent and selective inhibitor of the SARS-CoV-2 M<sup>pro</sup> is being developed as an oral treatment of COVID-19. Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of nirmatrelvir in order to increase plasma concentrations of nirmatrelvir to values that are sufficient to suppress viral replication through the entire dosing interval.

### 2.1. Study Rationale

The purpose of this study is to estimate the rBA of nirmatrelvir/ritonavir oral powder in 3 different food vehicles relative to the Paxlovid<sup>®</sup> tablets under fasted condition, and to estimate the effect of food on the rBA of the nirmatrelvir/ritonavir oral powder formulation in healthy adult participants. The study will also assess the safety, tolerability, and palatability of nirmatrelvir/ritonavir oral powder in healthy adult participants.

### 2.2. Background

In December 2019, COVID-19 was identified as a new, potentially fatal, respiratory infection caused by the novel coronavirus, SARS-CoV-2. The WHO declared COVID-19 a Public Health Emergency of International Concern on 30 January 2020 and further characterized the disease outbreak as a pandemic on 11 March 2020.<sup>1</sup>

Nirmatrelvir is an orally bioavailable 3CL<sup>pro</sup> inhibitor shown to be effective against SARS-CoV-2 3CL<sup>pro</sup> ( $K_i = 0.00311 \mu\text{M}$ ) in a biochemical enzymatic assay. Nirmatrelvir is being developed as an oral treatment in patients with COVID-19 infection.

Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of nirmatrelvir in order to increase plasma concentrations of nirmatrelvir to values that are sufficient to suppress viral replication through the entire dosing interval. Ritonavir is not expected to have any pharmacological impact on the SARS-CoV-2 virus and its elimination. Ritonavir is being used only as a PK boosting agent.

The clinical development program for nirmatrelvir includes 12 completed clinical studies: eight Phase 1 studies in healthy participants (C4671001, C4671008, C4671019, C4671024, C4671012, C4671013, C4671014 and C4671015), one Phase 1 study in renal impairment participants (C4671011), one Phase 1 study in hepatic impairment participants (C4671010) and two Phase 2/3 studies in COVID-19 patients (C4671005 and C4671006).

#### 2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of nirmatrelvir can be found in the current IB<sup>2</sup>.

#### 2.2.2. Nonclinical Pharmacokinetics and Metabolism

Hepatic CYP3A enzymes were identified as the main pathway for clearance of nirmatrelvir in vitro in liver microsomes (mouse, rat, hamster, rabbit, monkey, and human), hepatocytes (rat, monkey, and human), and in vivo in rat and monkey after repeat oral dosing. CCI

[REDACTED]

CCI [REDACTED]

Additional information of the nonclinical PK and metabolism of nirmatrelvir is available in the current IB<sup>2</sup>.

### 2.2.3. Nonclinical Safety

CCI [REDACTED]

Further details of the nonclinical safety program are provided in the current IB<sup>2</sup>.

### 2.2.4. Clinical Overview

Safety, tolerability and PK of nirmatrelvir were explored in Phase 1 studies in healthy adult participants (C4671001, C4671008, C4671012, C4671013, C4671014, C4671015, C4671019 and C4671024), as well as in renal impairment participants (C4671011) and hepatic impairment participants (C4671010). The relative bioavailability and food effect were evaluated in 2 Phase 1 studies (C4671001 and C4671019) in healthy volunteers. Efficacy and

safety of nirmatrelvir was evaluated in two interventional Phase 2/3 Studies (C4671005 and C4671006).

Included in this Clinical Overview are summaries of the results of Study C4671001, C4671019, C4671024, and C4671005.

Study C4671001 was a 5-part study consisting of SAD (PART-1), MAD (PART-2), relative bioavailability/food effect (PART-3), metabolism and excretion study (PART-4) and suprathreshold exposure cohort (PART-5). PART-1 and -2 are randomized, double-blind, sponsor-open, and placebo-controlled to evaluate safety, tolerability, and PK of single and multiple escalating oral doses of nirmatrelvir, respectively. PART-3 was randomized and open-label to evaluate relative bioavailability and food effect of an oral tablet formulation. PART-4 was an open-label, nonrandomized, single-period to evaluate the metabolism and excretion of nirmatrelvir. PART-5 was a double-blind, sponsor-open, randomized, crossover study to evaluate safety and tolerability at suprathreshold exposures.

C4671019 was a Phase 1, open-label, single dose, randomized, 2-treatment, 2-sequence, 2-period crossover study to evaluate the effect of a high-fat meal on the relative bioavailability of nirmatrelvir boosted with ritonavir following a single dose oral administration of nirmatrelvir in combination with ritonavir using CCI tablets of nirmatrelvir in healthy adult participants.

C4671024 was a Phase 1, open-label, single dose, randomized, crossover study in healthy adult participants to estimate rBA of nirmatrelvir/ritonavir CCI oral powder mixed with 3 different delivery vehicles (Test formulations) compared to the nirmatrelvir /ritonavir commercial tablets (Reference formulation) under fasted conditions.

C4671005 was a Phase 2/3 randomized, placebo-controlled trial in nonhospitalized adult participants with a laboratory-confirmed diagnosis of SARS-CoV-2 infection.

#### 2.2.4.1. Safety Overview

In the completed Phase 1 studies in healthy participants and Phase 2/3 study in participants with a laboratory-confirmed diagnosis of SARS-CoV-2 infection, nirmatrelvir/ritonavir was generally safe and well tolerated.

CCI



CCI



#### 2.2.4.2. Summary of Nirmatrelvir Pharmacokinetics in Human Study 1001- FIH

CCI



CCI



#### Study 1019-Food Effects

CCI



#### Study 1024-Relative Bioavailability for oral powder formulation

CCI



CCI



### 2.3. Benefit/Risk Assessment

Nirmatrelvir is not expected to provide any clinical benefit to healthy participants in this study. This study is designed primarily to further the understanding of human PK, metabolism, and elimination of nirmatrelvir.

Based on data from Study C4671001, C4671019, C4671024 and C4671005 and C4671006, the clinical safety profile of nirmatrelvir appears to be acceptable at single doses up to 1500 mg alone and up to 2250 mg administered with ritonavir (100 mg at -12h, 0h, 12h), split dosing administration (3 doses of 750 mg) at short intervals (approximately 2 hours from the previous dose), and at repeated daily doses administered orally for 10 days of up to 500 mg nirmatrelvir q12h with 100 mg ritonavir q12h.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of nirmatrelvir and ritonavir may be found in the IB<sup>2</sup>, 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
<b>Study Intervention: Nirmatrelvir</b>		
Dysgeusia	In Study C4671005, dysgeusia was recorded as an AE by 6% of participants receiving nirmatrelvir/ritonavir compared to <1% of participants receiving placebo	Participants may utilize recommendations to alleviate symptoms of dysgeusia while taking treatment such as peppermint post-dose. Dosing recommendations will be provided to the participant.
Emesis	Sporadic emesis was observed at $\geq 100$ mg/kg/day of nirmatrelvir in the 15-day NHP toxicology study.	AEs will be monitored and participants may receive antiemetics.
Hypertension	Transient increases in systolic, diastolic and mean BP were observed in pre-clinical 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.
<b>Study Intervention: Ritonavir</b>		
Gastrointestinal disturbances (including diarrhea, nausea, vomiting, and abdominal pain)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose of 100 mg used in this study. This is a single dose PK study. There will be close observation of AEs.
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 of 100 mg used in this study. There will be close observation of AEs.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 of 100 mg used in this study. There will be close observation of AEs and monitoring through 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 of 100 mg used in this study. There will be close observation of AEs. Fatigue (low energy or tiredness) will be assessed through collection of daily signs and symptoms and will also be assessed through physical examinations.
<b>Study Procedures</b>		
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

### 3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary:</b>	<b>Primary:</b>
<ul style="list-style-type: none"> <li>To estimate the rBA of the nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with water compared to the nirmatrelvir/ritonavir CCI [REDACTED] commercial tablets under fasted conditions.</li> <li>To estimate the rBA of the nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with infant formula compared to the nirmatrelvir/ritonavir CCI [REDACTED] commercial tablets under fasted conditions.</li> <li>To estimate the rBA of the nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with vanilla pudding compared to the nirmatrelvir/ritonavir CCI [REDACTED] commercial tablets under fasted conditions.</li> <li>To estimate the rBA of the nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with vanilla pudding under fed conditions compared to the nirmatrelvir/ritonavir CCI [REDACTED] commercial tablets under fasted conditions.</li> </ul>	<ul style="list-style-type: none"> <li>The test/reference ratios for <math>AUC_{inf}</math> (if data permits), <math>AUC_{last}</math>, and <math>C_{max}</math> of nirmatrelvir and ritonavir.</li> </ul>
<b>Secondary:</b>	<b>Secondary:</b>
<ul style="list-style-type: none"> <li>To estimate the effect of food on the rBA of the nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with vanilla pudding.</li> <li>To evaluate the safety and tolerability of nirmatrelvir/ritonavir in healthy participants.</li> <li>To assess the palatability of nirmatrelvir/ritonavir oral powder mixed with water/infant formula/vanilla pudding.</li> </ul>	<ul style="list-style-type: none"> <li>The test/reference ratios for <math>AUC_{inf}</math> (if data permits), <math>AUC_{last}</math>, and <math>C_{max}</math> of nirmatrelvir and ritonavir.</li> <li>Assessment of TEAEs, clinical laboratory abnormalities, vital signs, PEs, and 12 lead ECGs.</li> <li>Assessment of palatability via questionnaire: mouth feel, bitterness, tongue/mouth burn, throat burn and overall liking.</li> </ul>

Objectives	Endpoints
CCI [REDACTED]	[REDACTED]
I [REDACTED]	I [REDACTED]
I [REDACTED]	I [REDACTED]

## 4. STUDY DESIGN

### 4.1. Overall Design

This is a Phase 1, open-label, single dose, randomized, crossover study in healthy adult participants to estimate rBA of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed with 3 different food vehicles (Test formulations) compared to the nirmatrelvir/ritonavir CCI [REDACTED] commercial tablets (Reference formulation) under fasted conditions, and to estimate the effect of food on the rBA of the nirmatrelvir/ritonavir oral powder formulation mixed with vanilla pudding. The study will also assess the safety, tolerability, and palatability of nirmatrelvir/ritonavir in healthy adult participants.

Approximately 12 adult healthy male and/or female participants will be enrolled and randomized to 1 of 6 possible treatment sequences. Participants who discontinue from the study for non safety reasons may be replaced at the sponsor's discretion in collaboration with the investigator. The replacement participant will receive the same treatment sequences as the participant who discontinued.

Each enrolled participant will participate in 5 study periods to receive 5 different treatments according to the sequence determined by randomization:

- Treatment A: Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] tablets under fasted condition
- Treatment B: Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in water under fasted condition
- Treatment C: Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in infant formula under fasted condition
- Treatment D: Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in vanilla pudding under fasted condition

- Treatment E: Single oral dose of nirmatrelvir/ritonavir CCI [REDACTED] oral powder mixed in vanilla pudding under fed condition

Participants will be randomly assigned to 1 of 6 sequences as shown below in Table 3. Participants will be discharged on Day 4 of Period 5, following completion of all assessments. Between each treatment, a minimum of 4 days washout is proposed to minimize any residual nirmatrelvir concentrations prior to start of the next treatment. The total planned duration of participation from the Screening visit to the last follow-up phone call, is approximately 12 weeks.

**Table 3. Randomized Treatment Sequences**

Treatment Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
Sequence 1 (N = 2)	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E
Sequence 2 (N = 2)	Treatment B	Treatment C	Treatment A	Treatment D	Treatment E
Sequence 3 (N = 2)	Treatment C	Treatment A	Treatment B	Treatment D	Treatment E
Sequence 4 (N = 2)	Treatment A	Treatment C	Treatment B	Treatment E	Treatment D
Sequence 5 (N = 2)	Treatment B	Treatment A	Treatment C	Treatment E	Treatment D
Sequence 6 (N = 2)	Treatment C	Treatment B	Treatment A	Treatment E	Treatment D

Healthy participants will be screened to determine eligibility within 28 days prior to study treatment. Medical history and results of PE, vital signs, 12-lead ECG, and clinical laboratory evaluations will determine eligibility. Eligible participants will be admitted to the CRU on Period 1 Day -1 and will be confined in the CRU until discharge which is Day 4 of Period 5.

On Day 1 of each period, participants will receive a single oral dose of study interventions nirmatrelvir/ritonavir CCI [REDACTED] as per the randomization schedule. Study treatments A and D will be administered with approximately 240 mL of ambient temperature water and treatments B and C will be administered with approximately 210 mL of ambient temperature water under fasted conditions (10 hours overnight fast and no food until 4 hours after dosing). Study treatment E will be administered with approximately 240 mL of ambient temperature water approximately 30 minutes after the start of a standard high-fat, high-calorie breakfast. Serial PK samples will be collected up to 72 hours post dose. Participants will be discharged from the CRU on Period 5, Day 4 following completion of all assessments.

If a participant has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

A safety follow-up call will be made to participants approximately 28 to 35 days from administration of the final dose of study intervention.

## **4.2. Scientific Rationale for Study Design**

Nirmatrelvir/ritonavir oral powder is an alternative formulation for adult and pediatric patients who are not able to swallow nirmatrelvir/ritonavir commercial tablets. C4671024 study results showed nirmatrelvir exposure is higher for oral powder mixed with apple sauce and vanilla pudding compared to commercial tablets (data on file). Specifically nirmatrelvir  $C_{\max}$  was 61% (90% CI 46%, 79%) higher and  $AUC_{\inf}$  was 25% (90% CI 16%, 35%) higher for nirmatrelvir/ritonavir oral powder mixed with vanilla pudding compared to nirmatrelvir/ritonavir commercial tablets.

The objective of the study is to estimate the rBA of nirmatrelvir/ritonavir oral powder mixed with 3 different delivery vehicles (Test treatments) compared to nirmatrelvir/ritonavir commercial tablets (Reference treatment), and to estimate the effect of food on the rBA of the nirmatrelvir/ritonavir oral powder mixed with vanilla pudding. The study will also assess the safety, tolerability and palatability of nirmatrelvir/ritonavir oral powder in healthy adult participants.

Specifically for the food effect period of the study, the formulation to be tested should be administered on an empty stomach during one period and the high-fat meal during the alternate period. The FDA guidance for evaluation of a food effect on bioavailability recommends using meal conditions that are expected to provide the greatest effects on gastrointestinal physiology so that systemic drug availability is maximally affected. Therefore, a high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) meal will be used for the evaluation of food effect in this study.

The study is being designed as a crossover study to account for any period effect. Between each treatment, a minimum of 4 days washout is proposed to minimize any residual nirmatrelvir and ritonavir concentrations prior to start of the next treatment, as nirmatrelvir has a half-life of approximately 6 to 13 hours when co-administered with ritonavir.

### **4.2.1. Choice of Contraception/Barrier Requirements**

Human reproductive safety data are limited for nirmatrelvir, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see [Appendix 4](#)).

### **4.2.2. 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.

### 4.3. Justification for Dose

The dose of nirmatrelvir/ritonavir **CCI** for 5 days is the approved therapeutic dose and treatment duration under emergency use authorization. This dose is lower than the highest dose evaluated in the Phase 1 C4671001 study and is safe and well tolerated.

This study is designed to evaluate rBA of nirmatrelvir/ritonavir oral powder mixed with 3 different delivery vehicles compared to nirmatrelvir/ritonavir commercial tablet formulation in healthy adult participants at the approved therapeutic dose. The same dose was evaluated in C4671024 rBA study for oral powder. Therefore, a single oral dose nirmatrelvir/ritonavir **CCI** will be used in this rBA study.

### 4.4. End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the [SoA](#) for the last participant in the trial.

A participant is considered to have completed the study if they have completed all periods of the study, including the last scheduled procedure 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. Use of 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, and 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. Male and/or female participants must be  $\geq 18$  years of age, inclusive, at the time of signing the ICD.
  - Refer to [Appendix 4](#) for reproductive criteria for male (Section [10.4.1](#)) and female (Section [10.4.2](#)) participants.

### **Type of Participant and Disease Characteristics:**

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical exam, laboratory tests, vital signs and standard 12-lead ECG.
3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
4. Female participants of childbearing potential must have a negative pregnancy test.

### **Weight:**

5. BMI of 17.5 to 30.5 kg/m<sup>2</sup>; and a total body weight >50 kg (110 lb).

### **5.2. Exclusion Criteria**

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

#### **Medical Conditions:**

1. Positive test result for SARS-CoV-2 infection on Day -1.
2. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).
  - Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).
  - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb or HCVAb. Hepatitis B vaccination is allowed.
3. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study).

### **Prior/Concomitant Therapy:**

4. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Refer to Section 6.9 Prior and Concomitant Therapy for additional details.
  - Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of nirmatrelvir/ritonavir and during study treatment.
  - Concomitant use of any medications or substances that are inhibitors of CYP3A4 are prohibited during study treatment and 4 days after the last dose of study intervention.
5. Participants who have received a COVID-19 vaccine within 7 days before screening or admission, or who are to be vaccinated with a COVID-19 vaccine at any time during the study confinement period.

### **Prior/Concurrent Clinical Study Experience:**

6. Previous administration with an investigational drug 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). Participants who have participated in previous clinical trials with nirmatrelvir may be eligible to participate in this study as long as they meet all other criteria.

### **Diagnostic Assessments:**

7. A positive urine drug test.
8. Screening supine BP  $\geq 140$  mm Hg (systolic) or  $\geq 90$  mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is  $\geq 140$  mm Hg (systolic) or  $\geq 90$  mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.
9. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval  $>450$  msec, complete LBBB, signs of an acute, old or age indeterminate myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third -degree AV block, or serious brady arrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is  $>450$  msec, this interval should be rate -corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer -interpreted ECGs

should be overread by a physician experienced in reading ECGs before excluding a participant.

10. Participants with **ANY** of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

- AST **or** ALT level  $\geq 1.5 \times \text{ULN}$ ;
- T bili level  $\geq 1.5 \times \text{ULN}$ ; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is  $\leq \text{ULN}$ .
- eGFR  $< 60 \text{ mL/min/1.73 m}^2$  based on the CKD-EPI equation.

**Other Exclusion Criteria:**

11. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).
12. Use of tobacco or nicotine containing products in excess of the equivalents of 5 cigarettes per day or 2 chews of tobacco per day.
13. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
14. History of sensitivity to heparin or heparin-induced thrombocytopenia, nirmatrelvir, ritonavir, or any of the formulation components of nirmatrelvir, or ritonavir.
15. Unwilling or unable to comply with the criteria in the [Lifestyle Considerations](#) section of this protocol.
16. 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.
17. Pregnant or breastfeeding women.

### 5.3. Lifestyle Considerations

The following guidelines are provided:

#### 5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see [Appendix 4](#), Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in [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. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample on Day 1 of each Period.
- For the fed periods (Treatment E) only, on Day 1, following an overnight fast of at least 10 hours, participants should begin breakfast approximately 30 minutes prior to nirmatrelvir/ritonavir administration. The breakfast will be consumed over approximately a 20-minute interval with nirmatrelvir/ritonavir administered within approximately 10 minutes of completion of the meal. Participants should finish the entire breakfast.
- For the fasted periods (Treatment A;B;C;D) only, on Day 1, following an overnight fast of at least 10 hours, participants should take the medications.
- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.
- Lunch will be provided approximately 4 hours after nirmatrelvir/ritonavir dosing.
- Dinner will be provided approximately 9 to 10 hours after nirmatrelvir/ritonavir dosing.

- An evening snack may be permitted.
- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.
- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

### **5.3.3. Caffeine, Alcohol, and Tobacco**

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.
- Participants will abstain from alcohol for 24 hours prior to admission (or as specified above for red wine) to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Participants will abstain from the use of tobacco or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

### **5.3.4. Activity**

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted;
- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, PR, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after nirmatrelvir/ritonavir dosing;
- Participants will be confined to the procedure room for the first 1 hour after dosing on Day 1 of each period, except to use the bathroom. After this, participants may be ambulatory but should not engage in strenuous activities.

## **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. Screen failure data are collected and remain as source and are not reported on the CRF.

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

### 6.1. Study Intervention(s) Administered

Study Intervention(s)				
Intervention Name	Nirmatrelvir Tablets	Ritonavir Tablets	Nirmatrelvir Oral Powder	Ritonavir Oral Powder
Arm Name (group of participants receiving a specific treatment or no treatment)	nirmatrelvir/ritonavir commercial tablets	nirmatrelvir/ritonavir commercial tablets	nirmatrelvir/ritonavir oral powder	nirmatrelvir/ritonavir oral powder
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Powder	Powder
Unit Dose Strength(s)	CCl			
Dosage Level(s)	Single dose	Single dose	Single dose	Single dose
Route of Administration	Oral	Oral	Oral	Oral
IMP or NIMP/AxMP	IMP	NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided locally by the trial site	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a bulk container for dispensing into individual participant containers by the trial site	N/A	Study intervention will be provided in a bulk container for dispensing into individual participant containers by the trial site	Study intervention will be provided in a bulk container for dispensing into individual participant containers by the trial site
Former name	PF-07321332		PF-07321332	

Study Arm(s)					
Arm Title	Nirmatrelvir/ ritonavir commercial tablets	Nirmatrelvir/ ritonavir oral powder mixed with water	Nirmatrelvir/ ritonavir oral powder mixed with infant formula	Nirmatrelvir/ ritonavir oral powder mixed with vanilla pudding (fasted)	Nirmatrelvir/ ritonavir oral powder mixed with vanilla pudding (fed)
Arm Type	Reference	Experimental	Experimental	Experimental	Experimental
Arm Description	Single oral dose of nirmatrelvir/ ritonavir CCI commercial tablets under fasted conditions	Single oral dose of nirmatrelvir/ ritonavir CCI oral powder mixed with water under fasted conditions	Single oral dose of nirmatrelvir/ ritonavir CCI oral powder mixed with infant formula under fasted conditions	Single oral dose of nirmatrelvir/ritonavir CCI oral powder mixed with vanilla pudding under fasted conditions	Single oral dose of nirmatrelvir/ ritonavir CCI oral powder mixed with vanilla pudding under fed conditions

Nirmatrelvir CCI tablets and nirmatrelvir oral powder will be supplied to CRU in bulk along with individual dosing containers for unit dosing.

Ritonavir oral powder will be supplied to CRU in bulk along with individual dosing containers for unit dosing

Commercially available ritonavir CCI tablets will be sourced by the CRU.

Vehicles (infant formula and vanilla pudding) for nirmatrelvir and ritonavir oral powder administration will be sourced by the CRU.

### 6.1.1. Administration

Study interventions will be administered orally and according to the conditions described in the [SoA](#) section and Protocol Section [5.3.2 Meals and Dietary Restrictions](#).

Doses taken under fasted condition: On Day 1 of each treatment period, following an overnight fast of at least 10 hours, participants will receive nirmatrelvir CCI (as CCI tablets) with ritonavir CCI (as CCI tablet) with approximately 240 mL ambient temperature water or nirmatrelvir/ritonavir CCI oral powder mixed with either water or infant formula with approximately 210 mL ambient temperature water or nirmatrelvir/ritonavir CCI oral powder mixed with vanilla pudding with approximately 240 mL ambient temperature water administered orally starting at approximately 0800 hours (plus or minus 2 hours). The use of food vehicles for delivery of oral powder are not considered a fed condition. Nirmatrelvir and ritonavir tablets will be dosed simultaneously (within no more than 5 minutes of each other). Participants will swallow all tablet formulations whole and will not manipulate or chew the tablets prior to swallowing. Water will be withheld for 1 hour predose (with the exception of the water consumed as part of the breakfast) and 1 hour after the study treatment administration.

Doses taken under fed condition: On Day 1, following an overnight fast of at least 10 hours, participants will be administered the standard high-fat, high-calorie breakfast approximately

30 minutes prior to the administration of nirmatrelvir/ritonavir oral powder mixed with vanilla pudding. The entire breakfast will be consumed within approximately 20 minutes. The nirmatrelvir/ritonavir CCI oral powder mixed with vanilla pudding will be administered 30 minutes after the start of breakfast (allowable window approximately 30 minutes) with 240 mL ambient temperature water. Participants who do not finish the entire meal within approximately 20 minutes or who vomit after consuming the meal will not be dosed resulting in early termination from the study. No additional food will be allowed for at least 4 hours post-dose. Water will be withheld for 1 hour predose (with the exception of the liquid consumed as part of the breakfast) and 1 hour after the study treatment administration.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, PR, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after nirmatrelvir/ritonavir dosing.

## **6.2. Preparation, Handling, Storage, and Accountability**

1. The investigator or designee must confirm 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 for upon return to business.
4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the 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 CRU site procedures.
5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.
6. Study interventions should be stored in their original containers.

7. The investigator, institution, or the head of the medical institution (where applicable) or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.
8. Further guidance and information for the final disposition of unused study interventions are provided in the CRU's site procedures. 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.

#### **6.2.1. Preparation and Dispensing**

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Nirmatrelvir **CCI** tablets will be dispensed at the CRU into individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

Commercial ritonavir (Norvir® or other local commercialized product) oral tablets will be dispensed at the CRU into individual dosing containers using the package insert as guidance by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

Nirmatrelvir/ritonavir oral powder will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). Details of dose preparations, volume/amount of food vehicle, will be given in the EDR. Prepared doses will be labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

### 6.3. Assignment to Study Intervention

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

### 6.4. Blinding

This is an open-label study.

### 6.5. Study Intervention Compliance

As participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the CRU will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

### 6.6. Dose Modification

No dose modification is anticipated.

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

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

### 6.8. Treatment of Overdose

For this study, any dose of nirmatrelvir greater than **CCI** or ritonavir **CCI** within a 24-hour time period [ $\pm 2$  hours] 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 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 day from the date of the last dose of study intervention if requested by the 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 medical monitor as needed based on the clinical evaluation of the participant.

## **6.9. Prior and Concomitant Therapy**

Participants will abstain from all concomitant treatments, except for the treatment of adverse events and hormonal contraceptives that meet the requirements of this study in participants who are WOCBP (see [Appendix 4](#)).

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of  $\leq 1$  g/day.

As nirmatrelvir and ritonavir are both primarily metabolized by CYP3A4, concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to dosing of study intervention. Additionally, ritonavir and nirmatrelvir are inhibitors of CYP3A4. Therefore, medications highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events are not permitted during dosing of nirmatrelvir/ritonavir, through 4 days after the last dose of nirmatrelvir/ritonavir.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each site visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

### **6.9.1. Rescue Medicine**

There is no rescue therapy to reverse the AEs observed with nirmatrelvir or ritonavir; standard medical supportive care must be provided to manage the AEs.

## **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 requiring discontinuation in investigator's view;
- Pregnancy;
- Positive COVID-19 test.

If study intervention is permanently discontinued, the participant will not remain in the study for further evaluation. See the [SoA](#) for data to be collected at the time of discontinuation of study intervention.

#### **7.1.1. ECG Changes**

A participant who meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from the study intervention.

- QTcF >500 msec;
- Change from baseline: QTcF >60 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

#### **7.1.2. Potential Cases of Acute Kidney Injury**

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of  $\geq 0.3$  mg/dL (or  $\geq 26.5$   $\mu\text{mol/L}$ ) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of  $\geq 0.3$  mg/dL [or  $\geq 26.5$   $\mu\text{mol/L}$ ] in SCr relative to the participant's own baseline measurement) is  $\geq 0.4$  mg/dL (or  $\geq 35.4$   $\mu\text{mol/L}$ ), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If  $\geq 2$  healthy participants are noted to have 2 consecutive SCr results of  $\geq 0.3$  mg/dL (or  $\geq 26.5$   $\mu\text{mol/L}$ ), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

### 7.1.3. Stopping Rules

Dosing will be halted at any time if 1 of the following circumstances occurs and it is determined by the investigator that the occurrence is at least possibly related to the administration of study drug:

- A SAE (eg, a serious AE considered at least possibly related to study drug administration) in 1 participant.
- Severe NSAE (eg, severe NSAEs considered at least possibly related to study drug administration) in 2 participants, independent of whether it is within or not within the same SOC.

When stopping rules are met, a data review will be conducted by the sponsor and investigator. If integrated analysis of available data leads to the conclusion that further dosing is justified, an amendment to the protocol may be required if additional safety monitoring is warranted.

### 7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Investigator's decision;
- Pregnancy.

At the time of discontinuing from the study, 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.

The participant will be permanently discontinued from the study intervention and the study at that time.

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

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

#### **7.2.1. Withdrawal of Consent**

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with 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 he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone

calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

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

## **8. STUDY ASSESSMENTS AND PROCEDURES**

### **8.1. Administrative 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.

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

Adherence to the study design requirements, including those specified in the [SoA](#), is essential and required for study conduct.

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

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

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

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (PR and BP) should be collected prior to the insertion of the catheter.

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

The total blood sampling volume for individual participants in this study is approximately 350 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.

To prepare for study participation, participants will be instructed on the information in the [Lifestyle Considerations](#) and [Prior and Concomitant Therapy](#) sections of the protocol.

## **8.2. Efficacy Assessments**

Not applicable.

## **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. Physical Examinations**

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the [SoA](#). For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

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

#### 8.3.2.1. Blood Pressure and Pulse Rate

Supine BP, PR will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and PR is preferable; however, when done manually, PR will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

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](#).

#### 8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the [SoA](#) section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a post dose QTcF interval is increased by  $\geq 60$  msec from the baseline **and** is  $>450$  msec; or b) an absolute QT value is  $\geq 500$  msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a post dose QTcF interval remains  $\geq 60$  msec from the baseline **and** is  $>450$  msec; or b) an absolute QT value is  $\geq 500$  msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in [Appendix 8](#).

#### **8.3.4. Clinical Safety Laboratory Assessments**

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 48 hours 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.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

#### **8.3.5. COVID-19 Specific Assessments**

Participants will be tested for COVID-19 infection by RT-PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of  $4 \times 24$  hours in house), or if they develop COVID-19 like symptoms as per local procedures. Additional testing may be required by local regulations or by the PI.

### **8.3.6. Pregnancy Testing**

A serum 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](#). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. 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 the end of the study. 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.

### **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 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 CT SAE Report Form.

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

#### **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 on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in [Appendix 3](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

#### **8.4.1.2. Recording Nonserious AEs and SAEs on the CRF**

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

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

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 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, inhalation, or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact 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/participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a

follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly 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, inhalation, or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form 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 accord 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 CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

#### **8.4.6. Cardiovascular and Death Events**

Not applicable.

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

Not applicable.

#### **8.4.8. Adverse Events of Special Interest**

Not applicable.

##### **8.4.8.1. Lack of Efficacy**

This section is not applicable because efficacy is not expected in the study population.

#### **8.4.9. Medical Device Deficiencies**

Not applicable.

##### **8.4.9.1. Time Period for Detecting Medical Device Deficiencies**

Not applicable.

##### **8.4.9.2. Follow-Up of Medical Device Deficiencies**

Not applicable.

#### 8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

Not applicable.

#### 8.4.9.4. Regulatory Reporting Requirements for 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:

<b>Recorded on the Medication Error Page of the CRF</b>	<b>Recorded on the Adverse Event Page of the CRF</b>	<b>Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness</b>
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.

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 on a CT SAE Report Form **only when associated with an SAE**.

## 8.5. Pharmacokinetics

### 8.5.1. Plasma for Analysis of Nirmatrelvir and Ritonavir

Blood samples of approximately 4 mL, to provide approximately 1.5 mL plasma, will be collected for measurement of plasma concentrations of nirmatrelvir and ritonavir as specified in the [Table 2](#). 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 samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) 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. Collection of samples more than 10 hours after dose administration that are obtained  $\leq 1$  hour away from the nominal time relative to dosing 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.

Samples will be used to evaluate the PK of nirmatrelvir and ritonavir. CCI [REDACTED]

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

CCI [REDACTED]

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 determination as to whether sample integrity has been compromised.

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 archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed 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

A 4-mL blood sample optimized for DNA isolation **CCI** 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) CCI  
[REDACTED] Genes and other analytes (eg, proteins, RNA, nondrug 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 and supporting documentation.

## 8.7. Biomarkers

Biomarkers are not evaluated in this study.

### 8.7.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

### 8.7.2. Specified Protein Research

Specified protein research is not included in this study.

### 8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

CCI

11

## 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 are not evaluated in this study.

## 8.10. Taste Assessment of Nirmatrelvir Oral Powder

The sensory attributes of nirmatrelvir/ritonavir oral powder will be evaluated by the participant using a Palatability Questionnaire ([Appendix 9](#)) in the period when suspension may be administered. Participants will review the palatability questionnaire and instructions prior to the first taste assessment to Treatment B, C, and Don of Day 1 Period 1 or Period 2. Each participant will complete the palatability Survey immediately following dosing (within 1 min) and at 5, 10, and 20 minutes post oral administration of nirmatrelvir/ritonavir oral powder.

## 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.

### 9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

### 9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	“Enrolled” means a participant's agreement to participate in a clinical study following completion of the informed consent process and 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, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.
Safety Analysis Set	All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

Participant Analysis Set	Description
PK Concentration Set	All participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported.
PK Parameter Set	All participants who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of primary interest are reported.

### 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.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

CCI			

### 9.3.2. Statistical Methods for PK Data

For the primary objective, natural log transformed  $AUC_{inf}$  (if data permits),  $AUC_{last}$  and  $C_{max}$  will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within a sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. For primary objective, Treatment A will be the Reference treatment while Treatments B, C, D and E will be the Test treatments. For food effect estimation (periods 4 and 5 only) Treatment D will be the Reference treatment while Treatments E will be the Test treatment.

PK parameters, including plasma  $AUC_{inf}$  (if data permits),  $AUC_{last}$ ,  $C_{max}$ , CCI of nirmatrelvir and ritonavir will be summarized descriptively by treatment. For  $AUC_{inf}$  (if data permits),  $AUC_{last}$ , and  $C_{max}$ , a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for  $AUC_{inf}$  (if data permits),  $AUC_{last}$ , and  $C_{max}$ , will be plotted by treatment.

The plasma concentrations of nirmatrelvir and ritonavir will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant, as well as mean and median profiles of the plasma concentration time data will be plotted by treatment using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and semi-log scales.

Additional specifications about the tables, listings, and figures will be outlined in the SAP.

### 9.3.3. Other Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, PR, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and PE and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical

and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at Screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at Screening will be reported.

### 9.3.4. Other Analyse(s)

#### 9.3.4.1. Taste Assessment

The data collected for taste assessment using the sponsor-provided taste questionnaire will be numerically derived by measuring length (using a scale with gradations of at least 0.1 cm) of the “x” marked by the participant relative to the “good trait”. The taste attributes (bitterness, and tongue/mouth burn sensation) from the taste questionnaires ([Appendix 9](#)) will be listed and descriptively summarized and appropriate plots may be generated.

#### 9.3.4.2. Biomarker Assessment

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

### 9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development.

### 9.5. Sample Size Determination

A sample size of 12 participants will provide adequate precision to estimate the relative bioavailability and intrasubject variability nirmatrelvir. The following table presents the width of 90% CI for different estimated effects, with 80% coverage probability.

Parameter	Estimated Effect (100*Test/Reference)	90% CI		CI Width
AUC	85%	78.68	91.83	13.16
	90%	83.30	97.23	13.93
	95%	87.93	102.64	14.71
	100%	92.56	108.04	15.48
	105%	97.19	113.44	16.25
	110%	101.82	118.84	17.03
	115%	106.44	124.24	17.80
C <sub>max</sub>	85%	76.51	94.43	17.91
	90%	81.02	99.98	18.97
	95%	85.52	105.54	20.02
	100%	90.02	111.09	21.07
	105%	94.52	116.64	22.13
	110%	99.02	122.20	23.18
	115%	103.52	127.75	24.23

These estimates are based on the assumption that within-participant standard deviations are 0.102 and 0.139 for  $\ln C_{\max}$  and  $\ln AUC_{\inf}$ , respectively, as obtained from clinical Study C4671024 in healthy participants.

In addition, a sample size of 12 participants will provide adequate precision to estimate the relative bioavailability and intrasubject variability ritonavir. The following table presents the width of 90% CI for different estimated effects, with 80% coverage probability.

Parameter	Estimated Effect (100*Test/Reference)	90% CI		CI Width
AUC	85%	72.71	99.37	26.66
	90%	76.98	105.22	28.23
	95%	81.26	111.06	29.80
	100%	85.54	116.91	31.37
	105%	89.81	122.75	32.94
	110%	94.09	128.60	34.51
	115%	98.37	134.44	36.07
$C_{\max}$	85%	69.29	104.27	34.98
	90%	73.37	110.40	37.04
	95%	77.44	116.54	39.09
	100%	81.52	122.67	41.15
	105%	85.60	128.80	43.21
	110%	89.67	134.94	45.27
	115%	93.75	141.07	47.32

These estimates are based on the assumption that within-participant standard deviations are 0.206 and 0.269 for  $\ln AUC_{\inf}$  and  $\ln C_{\max}$ , respectively, as obtained from clinical Study C4671024 in healthy participants.

Participants who withdraw from the study or discontinue treatment, or whose PK samples are considered to be nonevaluable with respect to the primary PK objective may be replaced at the discretion of the investigator upon consultation with the sponsor.

## **10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

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

#### **10.1.1. Regulatory and Ethical Considerations**

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

#### **10.1.2. Financial Disclosure**

Not applicable.

#### **10.1.3. 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 and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

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

The participant must be informed that 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.

The participant 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 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 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.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 10 days from the previous ICD signature date.

#### **10.1.4. Data Protection**

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

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

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

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

The sponsor maintains 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 not use a E-DMC.

#### **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](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the EudraCT/CTIS, and/or [www.pfizer.com](http://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](http://www.clinicaltrials.gov)

Pfizer posts clinical trial results on [www.clinicaltrials.gov](http://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](http://www.pfizer.com)

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

Documents within marketing

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 and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

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

Monitoring details describing strategy, 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 [IQMP] 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's designee (Pfizer CRU).

Description of the use of the computerized system is documented in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

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 designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

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

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

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.

## 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.

**Table 5. Protocol-Required Safety Laboratory Assessments**

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN and creatinine	<u>Local Dipstick:</u>	<ul style="list-style-type: none"> <li>SARS-CoV-2 RT-PCR</li> <li>Urine drug screening<sup>b</sup></li> <li>Pregnancy test (<math>\beta</math>-hCG)<sup>c</sup></li> <li>eGFR [CKD-EPI]</li> </ul>
Hematocrit	Glucose (fasted)	pH <sup>e</sup>	
RBC count	Calcium	Glucose (qual)	
MCV	Sodium	Protein (qual)	
MCH	Potassium	Blood (qual)	
MCHC	Chloride	Ketones	
Platelet count	Total CO <sub>2</sub> (bicarbonate)	Nitrites	<u>At Screening only:</u>
WBC count	AST, ALT	Leukocyte esterase	<ul style="list-style-type: none"> <li>FSH<sup>d</sup></li> <li>HBsAg</li> <li>HbsAb<sup>f</sup></li> <li>HBcAb</li> <li>HCVAb</li> <li>HIV</li> </ul>
Total neutrophils (Abs)	Total bilirubin		
Eosinophils (Abs)	Alkaline phosphatase		
Monocytes (Abs)	Uric acid	<u>Laboratory:</u>	
Basophils (Abs)	Albumin	Microscopy <sup>a</sup>	
Lymphocytes (Abs)	Total protein		
	<u>Renal Function</u>		
	Cystatin C (Scys)		

- Microscopy only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
- The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
- Serum or urine  $\beta$ -hCG for female participants of childbearing potential.
- For confirmation of postmenopausal status only.
- Can be performed as per local procedures.
- HBsAb will be tested if HBsAg and/or HBcAb are positive.

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.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. **CCI**

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

#### 10.3.1. Definition of AE

AE Definition
<ul style="list-style-type: none"><li>• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.</li><li>• Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.</li></ul>

Events <u>Meeting</u> the AE Definition
<ul style="list-style-type: none"><li>• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:<ul style="list-style-type: none"><li>• Is associated with accompanying symptoms;</li><li>• Requires additional diagnostic testing or medical/surgical intervention;</li><li>• Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.</li></ul></li><li>• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.</li><li>• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.</li></ul>

<b>Events <u>NOT</u> Meeting the AE Definition</b>
<ul style="list-style-type: none"> <li>Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.</li> <li>The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.</li> <li>Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.</li> <li>Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).</li> <li>Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.</li> </ul>

### 10.3.2. Definition of an SAE

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

**d. Results in persistent or significant disability/incapacity**

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

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

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

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

**g. Other situations:**

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

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

**AE and SAE Recording/Reporting**

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

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

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

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

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

\*\*\* **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

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

#### **Assessment of Intensity**

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

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

#### **Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

#### **Follow-Up of AEs and SAEs**

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

#### 10.3.4. Reporting of SAEs

##### **SAE Reporting to Pfizer Safety via an Electronic DCT**

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

##### **SAE Reporting to Pfizer Safety via the CT SAE Report Form**

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

## **10.4. Appendix 4: Contraceptive and Barrier Guidance**

### **10.4.1. Male Participant Reproductive Inclusion Criteria**

No contraception methods are required for male participants in this study, as the calculated safety margin is  $\geq 100$ -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 she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

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

OR

- Is a WOCBP and agrees to use 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.

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 study treatment and until one menstrual cycle after stopping 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. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
  - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old 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 their 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 coadministered, a barrier method or other nonhormonal method of contraception must also be used if the participant is using estradiol-containing contraceptives.

## 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 study intervention 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

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

In some of DILI cases, elevations in AST and/or ALT may precede T bili elevations ( $>2 \times \text{ULN}$ ). Any substantial elevation in ALT, AST or bilirubin above baseline may be a potential DILI. The treating physician should report any elevations of concern—in some cases, elevation in ALT, AST  $2 \times \text{ULN}$  or T bili value  $1.5 \times \text{ULN}$  or less prompts treating physicians to consider hepatic injury. Hepatic injury may be from the study drug, a co-administered study drug or the disease under study.

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. The following criteria are of particular concern:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values  $\geq 3 \times \text{ULN}$  AND a T bili value  $\geq 2 \times \text{ULN}$  with no evidence of hemolysis and an alkaline phosphatase value  $< 2 \times \text{ULN}$  or not available (Hy’s law criteria).
- 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  $\geq 2$  times the baseline values AND  $\geq 3 \times \text{ULN}$ ; or  $\geq 8 \times \text{ULN}$  (whichever is smaller).
  - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of  $\geq 1 \times \text{ULN}$  **or** if the value reaches  $\geq 3 \times \text{ULN}$  (whichever is smaller).

Increases in AST/ALT and T bili should be assessed individually based on clinical judgment by the treating physician and their health care team; 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 for causality 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, CPK, 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 at time and dose of last dose of study intervention. 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 cases if no other reason for the LT abnormalities has yet been found. The treating physician is encouraged to consult with any other specialty that may assist in interpretation of the lab result or patient care management (eg, gastroenterologist, clinical pathologist, pharmacy, etc). **Such potential DILI cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LT abnormalities.**

A potential DILI 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: Kidney Safety: Monitoring Guidelines

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

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

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

### 10.7.2. Age-Specific Kidney Function Calculation Recommendations

#### 10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations<sup>3</sup>

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	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

#### **10.7.2.2. Adolescents (12 Years to <18 Years)—Cockcroft-Gault Formula**

CrCl (mL/min)

Males:  $\text{Cr/Cl} = [(140 - \text{age}) \times \text{body weight (in kg)}] / [\text{Scr (in mg/dL)} \times 72]$

Females:  $\text{Cr/Cl} = 0.85 \times [(140 - \text{age}) \times \text{body weight (in kg)}] / [\text{Scr (in mg/dL)} \times 72]$

#### **10.7.2.3. Children (2 Years to <12 Years)—Modified Schwartz Equation**

$\text{CrCl normalized to BSA (mL/min/1.73 m}^2\text{)} = (\text{K} \times \text{Ht}) / \text{Scr}$

Height (Ht) in centimeters; serum creatinine (Scr) in mg/dL.

K (proportionality constant): Female child < 12 years: K = 0.55. Male child <12 years: K = 0.70.

#### **10.7.2.4. Infants (1 Month to <2 Years) and Neonates (<1 Month)—Bedside Schwartz Equation**

$\text{eGFR (mL/min/1.73 m}^2\text{)} = 0.413 \times (\text{Ht/Scr})$

Height (Ht) in centimeters; serum creatinine (Scr) in mg/dL.

#### **10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities**

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

## 10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
<ul style="list-style-type: none"> <li>Marked sinus bradycardia (rate &lt;40 bpm) lasting minutes.</li> <li>New PR interval prolongation &gt;280 ms.</li> <li>New prolongation of QTcF to &gt;480 ms (absolute) or by <math>\geq 60</math> ms from baseline.</li> <li>New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate &lt;120 bpm.</li> <li>New-onset type I second-degree (Wenckebach) AV block of &gt;30 seconds' duration.</li> <li>Frequent PVCs, triplets, or short intervals (&lt;30 seconds) of consecutive ventricular complexes.</li> </ul>
ECG Findings That <u>May</u> Qualify as SAEs
<ul style="list-style-type: none"> <li>QTcF prolongation &gt;500 msec.</li> <li>New ST-T changes suggestive of myocardial ischemia.</li> <li>New-onset LBBB (QRS complex &gt;120 ms).</li> <li>New-onset right bundle branch block (QRS complex &gt;120 ms).</li> <li>Symptomatic bradycardia.</li> <li>Asystole: <ul style="list-style-type: none"> <li>In awake, symptom-free participants in sinus rhythm, with documented periods of asystole <math>\geq 3.0</math> seconds or any escape rate &lt;40 bpm, or with an escape rhythm that is below the AV node.</li> <li>In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.</li> <li>Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate &gt;120 bpm.</li> </ul> </li> <li>Sustained supraventricular tachycardia (rate &gt;120 bpm) ("sustained" = short duration with relevant symptoms or lasting &gt;1 minute).</li> </ul>

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

#### **ECG Findings That Qualify as SAEs**

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as “alerts” or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

## 10.9. Appendix 9: Palatability Questionnaire

### Nirmatrelvir/Ritonavir Oral Powder Palatability Questionnaire

1. Questionnaire should be filled out by adult participants, preferably with the assistance from clinician or a nurse.
2. Use **colored copy** of the Palatability Questionnaire.
3. **Do not alter (reduce or enlarge) the original size of the Palatability Questionnaire.**
4. Please collect the following background information:

#### Background Information

Study #/Study Site	
Period and Day	
Participant ID (Rand ID)	
Treatment	
Collect Date	
Questionnaire Fully Completed (circle one)	Yes/No

**Please answer the following questions and provide a mark (X) on the color bar at 1 (immediately), 5, 10 and 20 minutes after dosing. Please ensure participant has access to these descriptions when completing the questionnaire.**

**Q1: Mouth feel – Please tell us about the mouth feel (such as grittiness, stickiness, waxiness) of the product you tasted.**

**Q2: Bitterness – Please tell us about the degree of bitterness of the product you tasted.**

**Q3: Tongue/mouth burn – Please tell us about the degree of tongue/mouth burn of the product you tasted.**

**Q4: Throat burn – Please tell us about the degree of throat burn of the product you tasted.**

**Q5: Overall liking – Please indicate how much you like or dislike the product you tasted.**

**Example: How to provide a mark (×) on the color bar.**






**Good (score = 0)**



**Bad (score = 100)**






**Within 1 minute (immediately) after dosing**

**Provide a mark ( × ) on the color bar.**

	Mouth Feel	Bitterness	Tongue/Mouth Burn	Throat Burn	Overall Liking
<b>Good</b>					
<b>Bad</b>					






5 minutes after dosing

Provide a mark ( × ) on the color bar.

	Mouth Feel	Bitterness	Tongue/Mouth Burn	Throat Burn	Overall Liking
Good					
Bad					






**10 minutes after dosing**

**Provide a mark ( × ) on the color bar.**

	<b>Mouth Feel</b>	<b>Bitterness</b>	<b>Tongue/Mouth Burn</b>	<b>Throat Burn</b>	<b>Overall Liking</b>
<b>Good</b>					
<b>Bad</b>					

20 minutes after dosing

Provide a mark ( × ) on the color bar.

	Mouth Feel	Bitterness	Tongue/Mouth Burn	Throat Burn	Overall Liking
Good					
Bad					

**Additional Feedback** – After completing the “20 minute after dosing” palatability questions, please provide any additional descriptive feedback in the box below regarding the taste or odor of the product.

## 10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
	ongoing/continuous event
$^{19}\text{F}$ -NMR	$^{19}\text{F}$ nuclear magnetic resonance
$3\text{CL}^{\text{pro}}$	3C-like protein
Abs	absolute
ADL	activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$\text{AUC}_{\text{inf}}$	area under the concentration-time curve from time 0 extrapolated to infinity
$\text{AUC}_{\text{last}}$	area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration
AV	atrioventricular
AxMP	Auxiliary Medical Products
BBS	Biospecimen Banking System
$\beta$ -hCG	$\beta$ -human chorionic gonadotropin
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CCI	
$C_{\text{last}}$	last quantifiable concentration
$C_{\text{max}}$	maximum observed concentration
$\text{CO}_2$	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRU	clinical research unit

<b>Abbreviation</b>	<b>Term</b>
CSR	Clinical Study Report
CT	clinical trial
CTIS	Clinical Trial Information System
CTMS	Clinical Trial Management System
CYP	cytochrome P450
CYP2D6	cytochrome P450 2D6
CYP3A	cytochrome P450, family 3, subfamily A
CYP3A4	cytochrome P450 3A4
CYP3A5	cytochrome P450 3A5
DCT	data collection tool
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
E-DMC	External Data Monitoring Committee
E/T	early discontinuation
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
F/U	follow-up
FDA	Food and Drug Administration
FIH	first in human
$f_m$	fraction metabolized
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy

Abbreviation	Term
Ht	height
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation for Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
$\ln AUC_{inf}$	log-transformed $AUC_{inf}$
$\ln C_{max}$	log-transformed $C_{max}$
IND	Investigational New Drug
IPAL	Investigational Product Accountability Log
IQMP	Integrated Quality Management Plan
IRB	Institutional Review Board
IV	Intravenous(ly)
KDIGO	Kidney Disease Improving Global Outcomes
$k_{el}$	first order elimination rate constant
$k_i$	inhibition constant
LBBB	left bundle branch block
LT	liver test
$\ln AUC_{inf}$	log-transformed $AUC_{inf}$
$\ln C_{max}$	log-transformed $C_{max}$
$\text{Log}_e$	natural logarithm
LFT	liver function test
M-2	metabolite 2
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
$M^{pro}$	main protease
MQI	medically qualified individual
ms	millisecond
NA, N/A	not applicable
NHP	nonhuman primate
NIMP	noninvestigational medicinal product
NOAEL	No observed adverse effect level
NSAE	non-serious adverse event
NYHA	New York Heart Association
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PD	pharmacodynamic(s)
PE	physical examination
PI	principal investigator
PK	pharmacokinetic(s)
PR	pulse rate

Abbreviation	Term
PT/INR	prothrombin time-international normalized ratio
PVC	premature ventricular contraction/complex
q12h	every 12 hours
QTc	corrected QT interval
QTcF	QT corrected using Fridericia's formula
qual	qualitative
rBA	relative bioavailability
RBC	red blood cell
RT-PCR	reverse-transcriptase polymerase chain reaction
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	serum creatinine
Scys	serum cystatin C
SD	standard deviation
SE	supratherapeutic exposure
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
█	█
T bili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
CCI	█
ULN	upper limit of normal
US	United States
CCI	█
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

## 11. REFERENCES

---

- <sup>1</sup> World Health Organization. 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: 29 March 2020.
- <sup>2</sup> Investigator’s Brochure, nirmatrelvir. (Version 5.0)
- <sup>3</sup> Inker LA et al. N Engl J Med. 2021;385:1737-49.