Title Page

AN INTERVENTIONAL, EFFICACY AND SAFETY, PHASE 2, RANDOMIZED, DOUBLE-BLIND, 2-ARM STUDY TO INVESTIGATE A REPEAT 5-DAY COURSE OF NIRMATRELVIR/RITONAVIR COMPARED TO PLACEBO/RITONAVIR IN PARTICIPANTS AT LEAST 12 YEARS OF AGE WITH REBOUND OF COVID-19 SYMPTOMS AND RAPID ANTIGEN TEST POSITIVITY

Study Intervention Number:	PF-07321332
Study Intervention Name:	nirmatrelvir
US IND Number:	153517
EudraCT/EU CT Number:	2022-002827-36
ClinicalTrials.gov ID:	NCT05567952
Pediatric Investigational Plan Number:	not available
Protocol Number:	C4671042
Phase:	2
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title:

A Study to Learn About a Repeat 5-Day Treatment with Nirmatrelvir/Ritonavir in People with Return of COVID-19 Symptoms and SARS-CoV-2 Positivity After Finishing Treatment with Nirmatrelvir/Ritonavir

Document History

Document	Version Date
Amendment 4	29 June 2023
Amendment 3	12 May 2023
Amendment 2	01 February 2023
Amendment 1	16 September 2022
Original protocol	05 August 2022

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

Protocol Amendment Summary of Changes Table

Amendment 4 (29 June 2023)

Overall Rationale for the Amendment: The protocol was primarily amended to add secondary analyses for the primary and secondary efficacy endpoints using the new analysis set (mITT1). Additional revisions are noted in the table below.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Additional secondary analyses for primary and secondary efficacy endpoints using the new analysis set (mITT1). Update the multiplicity adjustment accordingly.	Based on regulatory feedback on the definition of the study analysis set.	Section 9.1.2 Multiplicity Adjustment Section 9.2 Analysis Sets Section 9.3.2.2 Main Analytical Approach Section 9.3.3.1 Time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart through Day 28 Section 9.3.3.2 Time (days) to sustained alleviation of all targeted signs and symptoms through Day 28
Non-substantial Modification(s)		
Minor editorial updates.	To correct grammatical and formatting errors, and to maintain consistency.	Throughout the protocol

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

An Interventional, Efficacy and Safety, Phase 2, Randomized, Double-Blind, 2-Arm Study to Investigate a Repeat 5-Day Course of Nirmatrelvir/Ritonavir Compared to Placebo/Ritonavir in Participants at Least 12 Years of Age with Rebound of COVID-19 Symptoms and Rapid Antigen Test Positivity

Brief Title:

A Study to Learn About a Repeat 5-Day Treatment with Nirmatrelvir/Ritonavir in People with Return of COVID-19 Symptoms and SARS-CoV-2 Positivity After Finishing Treatment with Nirmatrelvir/Ritonavir

Regulatory Agency Identification Number(s):

US IND Number:	153517
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Rationale:

Case reports in the literature describe individuals who have experienced symptomatic relapses of SARS-CoV-2 infection following completion of a 5-day course of nirmatrelvir/ritonavir. In the available cases, patients are described as experiencing rapid improvement in systemic symptoms following initiation of treatment but then experience a rebound in COVID-19 symptoms after completing therapy. The time course of symptom rebound suggests that symptom recurrence is likely not related to re-exposure and it does not reflect a potential re-infection event. In one case report, symptom relapse was accompanied by fluctuating RT-PCR cycle thresholds and antigen testing suggesting the potential for a rebound in viral replication. In a separate case series of 7 patients with recurrent symptoms, median SARS-CoV-2 RNA at baseline was 6.1 $\log_{10}$ copies/mL (range 4.2-7.3) and enrollment viral cultures were positive in 3 of 7 individuals. Several of the published case reports on symptom recurrence included viral sequencing and these reports to date have not identified resistance mutations to nirmatrelvir.

A retrospective review of 483 high-risk patients treated with nirmatrelvir/ritonavir reported 4 (0.8%) patients who experienced rebound of symptoms. Median time to rebound in this study was 9 days and rebound symptoms were characterized as mild and resolving without additional COVID-19 therapy with no patient requiring hospitalization.

Post-treatment increases in SARS-CoV-2 RNA levels (ie, viral RNA rebound) in nasopharyngeal samples were observed on Day 10 or Day 14 in a subset of nirmatrelvir/ritonavir and placebo recipients in the EPIC-HR study. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters but was generally similar among nirmatrelvir/ritonavir and placebo recipients, regardless of the rebound definition used. A similar or smaller percentage of placebo recipients compared to nirmatrelvir/ritonavir recipients had nasopharyngeal viral RNA results <LLOQ at all study timepoints in both the treatment and post-treatment periods. Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of nirmatrelvir/ritonavir treatment. Post-treatment viral RNA rebound also was not associated with drug resistance as measured by mPro sequencing. The clinical relevance of post-treatment increases in viral RNA following nirmatrelvir/ritonavir or placebo treatment is unknown.

At present, there are no controlled efficacy and safety data of a repeat 5-day course of nirmatrelvir/ritonavir in participants with acute rebound in symptoms and SARS-CoV-2 infection. Recurrence in symptoms along with a positive rapid antigen test following the completion of a 5-day course of nirmatrelvir/ritonavir may indicate that these patients may require additional therapy to achieve sustained viral clearance. Such patients may benefit from an additional 5-day treatment duration. The purpose of this study is to evaluate the efficacy, safety and tolerability of a second 5-day treatment course of nirmatrelvir/ritonavir in participants with a rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks (14 days) following completion of an initial 5-day treatment course.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on viral RNA level in NP swabs in participants with mild-to-moderate COVID-19.	• The change in viral SARS-CoV-2 RNA level as measured in NP swabs from baseline to Day 5.	• The difference in mean change of SARS-CoV-2 RNA level in NP swabs from baseline to Day 5 between nirmatrelvir/ritonavir and placebo/ritonavir group in patients with a rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course ,who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on the duration of viral shedding.	• Time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2) h apart through Day 28.	• The hazard ratio for time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2) h apart through Day 28 between nirmatrelvir/ritonavir and placebo/ritonavir group in patients with rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on the duration and severity of signs and symptoms in participants with mild-to-moderate COVID-19.	• Time (days) to sustained alleviation of all targeted signs and symptoms through Day 28 where sustained alleviation is defined as the first of 2 consecutive days when any symptoms scored as moderate or severe at baseline are scored as mild or absent and any symptoms scored as mild or absent at baseline are scored as absent.	• The hazard ratio for time to sustained alleviation of all targeted signs and symptoms through Day 28 between nirmatrelvir/ritonavir and placebo/ritonavir group in patients with rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.
• To describe the safety and tolerability of nirmatrelvir/ritonavir in participants with mild-to-moderate COVID-19.	• Incidence of TEAEs. Incidence of SAEs and AEs leading to discontinuation.	• Not applicable.

Overall Design:

This Phase 2, randomized, double-blind, placebo-controlled study will evaluate the efficacy and safety of a repeat 5-day treatment course of nirmatrelvir/ritonavir or placebo/ritonavir for the treatment of mild-to-moderate COVID-19. Participants must have written documentation, such as an electronic health record, medical record, or prescription receipt of treatment with nirmatrelvir/ritonavir (verbal assertion of treatment is not acceptable) with patient-reported 100% compliance (ie, completed a 5 day course of nirmatrelvir/ritonavir). They must have experienced alleviation or resolution in COVID-19 signs/symptoms followed by a worsening (rebound) of signs/symptoms along with a positive rapid antigen test **after** completing an initial 5-day course of nirmatrelvir/ritonavir.

The onset of rebound in COVID-19 symptoms along with evidence of SARS-CoV-2 infection must occur within 2 weeks (14 days) **after** completion of an initial 5-day course of nirmatrelvir/ritonavir. A 2-week time-period for rebound symptoms and SARS-CoV-2 infection was selected to enroll a population that has a presumptive recurrence of the same

viral illness and not a new SARS-CoV-2 infection. Symptom burden including alleviation, resolution and worsening (rebound) to qualify for the study is based on the judgment of **both** the participant along with investigator judgment.

Eligible participants for this study will be randomly assigned (2:1 allocation of active to placebo) to receive:

- nirmatrelvir plus ritonavir orally q12h for 5 days; or
- placebo plus ritonavir orally q12h for 5 days.

Randomization will be stratified by geographic region.

Participants will be screened within 24 hours before randomization.

Participants must be randomized within 48 hours from the onset of the rebound COVID-19 symptoms and must be randomized within 24 hours of a positive baseline rapid antigen test. The total study duration is up to 24 weeks, including study intervention administration through Day 5 or Day 6, efficacy and safety assessments through Day 34, and long-term follow up at Weeks 12 and 24.

Participants are eligible if they are at least 12 years of age (and weigh ≥40 kg at screening) and they must have at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19. However, participants who are immunocompromised are excluded from this study as they may have prolonged viral shedding due to their immunocompromised state. Participants will be eligible for enrollment irrespective of COVID-19 vaccination/boosted status (except for time course restrictions listed in the exclusion criteria).

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

Number of Participants:

Approximately 411 participants will be enrolled in the study.

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

Study Population:

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

1. Participants aged 12 years or older and weighing ≥40 kg at screening.

2. Participants must have written documentation with patient-reported 100% compliance (ie, completed a 5 day course of nirmatrelvir/ritonavir). They must have symptom alleviation or resolution in COVID-19 signs/symptoms followed by a worsening (rebound) of signs/symptoms after completing an initial 5-day course of nirmatrelvir/ritonavir based on the judgement of both the participant and investigator.

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

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

5. SARS-CoV-2 infection as determined by rapid antigen testing in any specimen collected within 24 hours prior to randomization and collected within 2 weeks (14 days) after the completion of the initial 5-day treatment course of nirmatrelvir/ritonavir.

6. Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19.

Exclusion Criteria

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

1. Current need for hospitalization, hospitalized for the index COVID-19 infection, or anticipated need for hospitalization within 24 h after randomization in the clinical opinion of the site investigator.

2. History of severe chronic liver disease (eg, jaundice, ascites, hepatic encephalopathy, history of bleeding esophageal or gastric varices). No laboratory testing is needed.

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

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

5. Receiving dialysis or eGFR <30 mL/min/1.73 m^2 (for adults) or eCrCl <30 mL/min (for adolescents) at screening using creatinine point of care device.

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

7. Immunocompromised.

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

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

10. COVID-19 vaccination within 14 days prior to study entry or anticipated COVID-19 vaccination through Day 34.

11. Receiving other COVID-19 specific treatments within 30 days of randomization and through Day 34, excluding the initial course of nirmatrelvir/ritonavir as well as blinded study medication.

12. Prior participation in this trial.

13. Current or previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

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

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

Study Arms and Duration:

Eligible participants for this study will be randomly assigned (2:1) to receive nirmatrelvir plus ritonavir orally q12h or placebo/ritonavir as specified in the tables below.

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

Study Arm(s)		
Arm Title	Nirmatrelvir/ritonavir	Placebo/ritonavir
Arm Type	Experimental	Other
Arm Description	Participants will receive nirmatrelvir/ritonavir 300 mg/100 mg (or 150 mg/100 mg for participants with eGFR ≥30 to <60 mL/min/1.73 m^2 or eCrCl ≥30 to <60 mL/min) q12h from Day 1 through Day 5.	Participants will receive placebo 0 mg/ritonavir 100 mg q12h for 5 days.

Statistical Methods:

The study will randomize approximately 411 participants in a 2:1 randomization ratio to nirmatrelvir/ritonavir or placebo/ritonavir.

The primary efficacy endpoint is the change in viral SARS-CoV-2 RNA level from baseline to Day 5 as measured in NP swabs. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.

With respect to the primary endpoint of change in SARS-CoV-2 RNA level from baseline to Day 5 as measured in NP swab in the mITT analysis set, and assuming a SD of 1.8 (based on Study C4671005 [EPIC-HR, NCT04960202]), a sample size of approximately 315 evaluable participants (210 participants in the nirmatrelvir/ritonavir group and 105 participants in the placebo/ritonavir group) is expected to provide 90% power to detect a difference of 0.7 $\log_{10}$ copies/mL in viral RNA between groups using a 2-sided 0.05 alpha level test. Assuming approximately 10% of participants will have a negative viral RNA result at baseline, and assuming a non-evaluable rate of 15%, approximately 411 participants will be randomized in the study to achieve approximately 315 participants evaluable for the primary efficacy endpoint.

No formal interim analysis is planned for this study. However, the sponsor may conduct unblinded reviews of the data during the course of the study if requested by regulatory

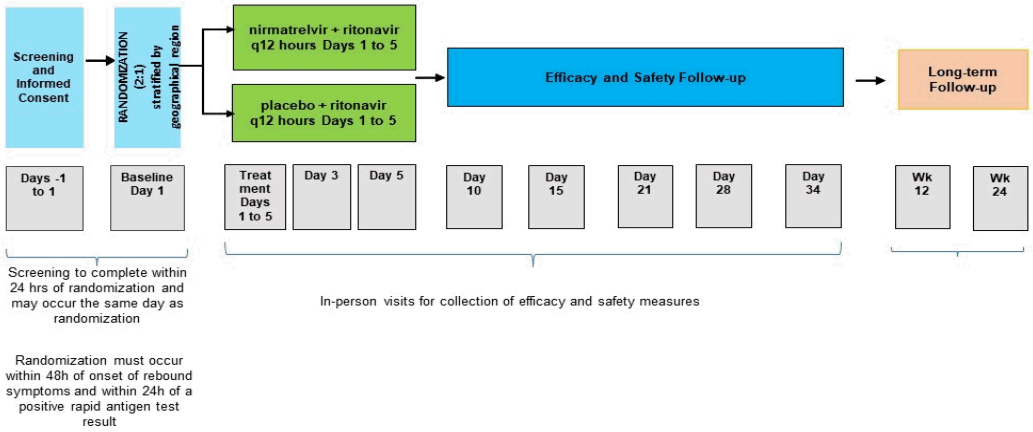
authorities including in the support of regulatory submissions. Should an unblinded review be requested, details of the unblinding plan will be described in the SAP and a separate data unblinding document.

Ethical Considerations:

Previous studies have demonstrated efficacy, safety, and tolerability of nirmatrelvir/ritonavir in adults at increased risk of progressing to severe COVID-19 illness. The FDA has granted EUA for nirmatrelvir/ritonavir for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. The most common adverse events described with nirmatrelvir/ritonavir treatment are allergic reactions, change in taste, diarrhea, headache, and vomiting. At present, there are no controlled efficacy and safety data of a repeat 5-day course of nirmatrelvir/ritonavir in participants with acute rebound in symptoms and SARS-CoV-2 infection. People who have rebound in mild-to-moderate COVID-19 may benefit from a repeat 5-day treatment course of nirmatrelvir/ritonavir. Considering the measures to minimize risk to study participants, the potential risks identified in association with nirmatrelvir/ritonavir are justified by the anticipated benefits that may be afforded to participants eligible for enrollment in this study.

Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants must avoid use of a non-study COVID-19 antiviral (excluding a single 5-day treatment course of nirmatrelvir/ritonavir for eligibility), monoclonal antibody therapy for COVID-19, or COVID-19 vaccination within 14 days prior to randomization and through completion of Day 34. Participants who progress to severe or critical COVID-19 will however be permitted to receive specific COVID-19 treatment(s) such as antiviral therapy or use of other treatments considered standard of care. Female participants who are not pregnant and are of childbearing potential must agree to use appropriate contraception methods.

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed 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	Screen	Treatment Period			Efficacy and Safety Follow-up Period					LTFU			Notes
Abbreviations used in this table may be found in Appendix 12.		Baseline (Day 1)	Day 3	Day 5	Day 10	Day 15	Day 21	Day 28	Day 34	Week 12	Week 24	ET (prior to Day 34)	• Day relative to start of study intervention (Day 1). • Baseline (Day 1) visit is a mandatory visit. • Assessments indicated in brackets [X] are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
Study Visit Location	**S**	**S**	**S/P**	**S/P**	**S/P**	**S/P**	**S/P**	**S/P**	**S/P**	**T**	**T**	**S/P**	• Site staff should, in discussion with participants, determine the most appropriate location to conduct study visits. Visits should take place at the investigational site (S). If this is not feasible, then alternate venues may include the participant's location (P). • If an in-person visit is held at a location other than S, the HCP performing the visit may be unable to complete all assessments. In these cases, a telemedicine/telehealth visit should also occur to perform the remaining assessments.
ELIGIBILITY													

Table 1. Study Schedule of Assessment

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Abbreviations used in this table may be found in Appendix 12.		**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 15**	**Day 21**	**Day 28**	**Day 34**	**Week 12**	**Week 24**	**ET (prior to Day 34)**	• Day relative to start of study intervention (Day 1). • Baseline (Day 1) visit is a mandatory visit. • Assessments indicated in brackets [X] are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
Informed consent/assent	X												• Informed consent/assent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
Verify inclusion/exclusion criteria	X												• See Section 5.1 and Section 5.2. • Screening visit: A serum creatinine point-of-care device assessment for calculating eGFR for adults 18 years and older, and eCrCl for adolescents 12 years to <18 years is required for eligibility (Appendix 7).
Demographics and medical history	X												• See Section 8.1.1.1. • Includes history of confirmed/presumed prior COVID-19 infections, including most recent infection, SARS-CoV-2 test results, if available, and COVID-19 vaccinations.
Physical Examination and Vital Signs													
Targeted physical examination	X												• See Section 8.3.1 for additional information.
Weight, height	X												• Height may be self-reported for participants ≥18 years of age. • See Section 8.3.1 for additional information.
Vital signs	X	X	X	X	X				X			X	• See Section 8.3.2 for additional information.

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Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
Laboratory Assessments													• See Section 8.3.3 for additional information. • See Appendix 2 for a list of Clinical Laboratory tests to be done. • For laboratory collection volumes, see the laboratory manual.
Hematology		X		X					X			X	• Baseline laboratory assessments should be collected prior to first dose of study intervention. • If deemed necessary to confirm eligibility, laboratory assessments at screening may be performed at the local laboratory at the investigator's discretion. • Abnormal laboratory valued related to AEs should be followed until resolution.
Blood chemistry		X		X					X			X	
Point-of-care serum creatinine assessment	X	[X]											• Screening visit: A serum creatinine point-of-care device assessment for determining estimation of kidney function (eGFR for adults 18 years and older, and eCrCl for adolescents 12 years to <18 years) is required for eligibility. See Section 10.7 for age specific kidney function calculations. • Baseline visit assessment expected only if screening and baseline visits are held on different days. If a serum creatinine point-of-care device assessment is performed at

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Visit Identifier	Screen	Treatment Period			Efficacy and Safety Follow-up Period					LTFU			Notes
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Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
													screening and baseline, the baseline estimate of kidney function will determine eligibility. • See Section 8.3.2.4.
FSH	X												• FSH is to be performed locally to confirm postmenopausal status in female participants <60 years of age at screening who are not using hormonal contraception or hormonal replacement therapy. Female participants aged 50 to 60 years with no menses for 12 months do not need FSH testing to be performed to confirm postmenopausal status. • See Appendix 2.
HIV test (Germany only)	X												• Local HIV testing at screening will be performed for participants in Germany as required by the German HA • See Appendix 2
Pregnancy Test	X								X			X	• See Section 8.3.4.
SARS-CoV-2 Serology		X		X				X				X	
Biomarker Assessments													
NP swab collection for SARS-CoV-2 RNA level		X	X	X	X	X	X	X	X			X	• All NP swabs of both nares, will be collected by HCP at visits indicated. Samples will be shipped to central lab for quantitative SARS-CoV-2 RNA concentration.

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Visit Identifier	Screen	Treatment Period			Efficacy and Safety Follow-up Period					LTFU			Notes
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Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
													• At Screening and Baseline (Day 1) only, rapid antigen testing can be done before NP swab collection. • At all other time points, NP swab collection will be collected **PRIOR** to the sample for rapid antigen testing. • See Section 8.7.1.
Rapid antigen testing (on site)	X	X	X	X	X	X	X	X	X			X	• Investigative sites will use test kits provided by the sponsor and perform sample collection and testing according to manufacturer's instructions. • At Screening and Baseline (Day 1) only, rapid antigen testing can be done before NP swab collection. • At all other time points rapid antigen testing must occur after NP swab collection. • Screening assessment performed locally, at site. If rapid antigen testing is performed at screening and baseline, the baseline result will determine eligibility. • Site staff should train participants/caregiver at the screening/baseline visit to ensure participants can perform the rapid antigen test appropriately. The participant should perform the baseline rapid antigen testing assessment

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Visit Identifier	Screen	Treatment Period			Efficacy and Safety Follow-up Period					LTFU			Notes
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Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
													during the visit to ensure proper sample collection under observation by site staff. • Will be self-collected by the participant. • See Section 8.1.3. • See Section 8.7.3.
Participant self-collected rapid antigen testing		Collected daily and witnessed by the site staff.*										•	• Site staff should train participants/caregiver at the screening/baseline visit to ensure participants can perform the rapid antigen test appropriately. The participant should perform the baseline rapid antigen testing assessment during the visit to ensure proper sample collection. • Only 1 rapid antigen test is expected to be performed daily. When onsite, rapid antigen testing will be done at the site and no self-collected rapid antigen testing at home will be done. • Site staff will observe the participant performing the rapid antigen test (ie, via video or videoconferencing software if the procedure is conducted remotely), confirm testing, and record the test result in the CRF. • *Daily testing will stop once the participant has 2 consecutive negative tests separated by at least 24[-2]h. Thereafter, rapid antigen

Table 1. Study Schedule of Assessment

Visit Identifier	Screen	Treatment Period			Efficacy and Safety Follow-up Period					LTFU			Notes
Abbreviations used in this table may be found in Appendix 12.		Baseline (Day 1)	Day 3	Day 5	Day 10	Day 15	Day 21	Day 28	Day 34	Week 12	Week 24	ET (prior to Day 34)	• Day relative to start of study intervention (Day 1). • Baseline (Day 1) visit is a mandatory visit. • Assessments indicated in brackets [X] are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
													testing will be done at regularly scheduled onsite visits. • See Section 8.1.3
Oropharyngeal samples for SARS-CoV-2 RNA level		X		X		X		X	X			X	• See Section 8.7.4.
Plasma collection for SARS-CoV-2 RNA level		X	X	X	X	X	X	X	X			X	• See Section 8.7.2.
Plasma collection specific for biomarkers		X		X		X		X	X			X	• See Section 8.7.6.1 .
Retained research samples for genetics (Prep D1)		X		X		X			X			X	• If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • See Section 8.6.2.
Retained research samples for biomarkers (Prep B2.5, Prep R1), M3 (urine)		X		X		X			X			X	• See Section 8.7.8
Study Intervention													
Randomization		X											

Table 1. Study Schedule of Assessment

Visit Identifier	Screen	Treatment Period			Efficacy and Safety Follow-up Period					LTFU			Notes
Abbreviations used in this table may be found in Appendix 12.		**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 15**	**Day 21**	**Day 28**	**Day 34**	**Week 12**	**Week 24**	**ET (prior to Day 34)**	• Day relative to start of study intervention (Day 1). • Baseline (Day 1) visit is a mandatory visit. • Assessments indicated in brackets [X] are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
Study intervention dispensation		X											• Study intervention will be dispensed on Day 1. (See Section 6.1.1) • See Appendix 7 for age-specific kidney function calculations to determine nirmatrelvir dosing.
Study intervention administration		Days 1 through 5											• Baseline assessments should be performed before administration of the first study intervention. • The first dose of study intervention will be administered to all participants on Day 1 during the in-person visit. All subsequent doses of study intervention will be self-administered (or administered to the participant by a legal guardian or caregiver). If only 1 dose of study intervention is administered on Day 1, study intervention should end on Day 6. • See Section 6.1.
Participant-completed study intervention log		Daily on Days 1 through 5											• Participants will use a participant-completed electronic dosing diary to record the date and time of their study intervention dosing. • Study intervention log should be completed daily on Days 1 through 6 if only 1 dose was administered on Day 1. • See Section 6.5.

Table 1. Study Schedule of Assessment

Visit Identifier	Screen	Treatment Period			Efficacy and Safety Follow-up Period					LTFU			Notes
Abbreviations used in this table may be found in Appendix 12.		**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 15**	**Day 21**	**Day 28**	**Day 34**	**Week 12**	**Week 24**	**ET (prior to Day 34)**	• Day relative to start of study intervention (Day 1). • Baseline (Day 1) visit is a mandatory visit. • Assessments indicated in brackets [X] are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
Staff review of study intervention log		Daily on Days 1 through 5											• Staff review of the study intervention log should be completed daily on Days 1 through 6 if only 1 dose was administered on Day 1. • See Section 6.
Study Intervention Accountability													
Retrieval of unused study intervention and empty study intervention containers				X									• If the last dose of study intervention is taken on Day 6, collect at next visit.
Study intervention accountability				X									• Study intervention accountability is only performed at the Day 10 visit if the last dose of study intervention is taken on Day 6.
Patient Reported Outcomes													
Participant-completed study diary (COVID-19 signs and symptoms)		Collected daily from Days 1 through 28.											• See Section 8.2.3.5.

Table 1. Study Schedule of Assessment

Visit Identifier	Screen	Treatment Period			Efficacy and Safety Follow-up Period					LTFU			Notes
Abbreviations used in this table may be found in Appendix 12.		**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 15**	**Day 21**	**Day 28**	**Day 34**	**Week 12**	**Week 24**	**ET (prior to Day 34)**	• Day relative to start of study intervention (Day 1). • Baseline (Day 1) visit is a mandatory visit. • Assessments indicated in brackets [X] are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
Collection of global impression questions		Collected daily from Days 1 through 28.											• Participants will answer 3 global impression questions. The global impression questions will be answered after the completion of the COVID-19 signs and symptoms diary is completed. • See Section 8.2.3.1.
SF-36 v2 Health Survey (Acute Form)		X						X		X	X		• Only adult participants (≥18 years of age at the time of screening) will be asked to complete the SF-36. See Section 8.2.3.2.
WPAI				X		X				X	X		• Only adult participants (≥18 years of age at the time of screening) will be asked to complete the WPAI. See Section 8.2.3.3
EQ-5D-5L		X		X		X			X	X	X		• Only adult participants (≥18 years of age at the time of screening) will be asked to complete the EQ-5D-5L. See Section 8.2.3.4.
Study Procedures and Assessments													
Provide participants with study emergency contact card	X												• See Section 10.1.11.
Collect/update secondary contacts		X							X				• See Section 8.1.1.2.

Table 1. Study Schedule of Assessment

Visit Identifier	Screen	Treatment Period			Efficacy and Safety Follow-up Period					LTFU			Notes
Abbreviations used in this table may be found in Appendix 12.		Baseline (Day 1)	Day 3	Day 5	Day 10	Day 15	Day 21	Day 28	Day 34	Week 12	Week 24	ET (prior to Day 34)	• Day relative to start of study intervention (Day 1). • Baseline (Day 1) visit is a mandatory visit. • Assessments indicated in brackets [X] are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
Record/update household characteristics		X		X	X	X	X	X	X			X	• See Section 8.1.2.
Record COVID-19-related medical visits			X	X	X	X	X	X	X			X	• COVID-19-related medical visits a participant has attended since the last assessment will be collected. • See Section 8.2.2.
Contraception check	X	X	X	X	X	X	X	X	X			X	• See Section 5.3.1 and Appendix 4.
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X			X	• All prescription and over-the-counter medications including vaccines taken by the participant within 30 days before study entry (considered prior treatment) will be recorded. Includes documentation along with start/stop dates of recent nirmatrelvir/ritonavir. • See Section 6.9.
COVID-19 adjunctive therapeutic procedures	X	X	X	X	X	X	X	X	X			X	• Nondrug treatments will be collected through the Day 34 visit or at the ET visit.
COVID-19 signs and symptoms										X	X		• See Section 8.2.3.5.
Vital Status Check										X	X		• Verify mortality status of participants.

Table 1. Study Schedule of Assessment

Visit Identifier	Screen	Treatment Period			Efficacy and Safety Follow-up Period					LTFU			Notes
Abbreviations used in this table may be found in Appendix 12.		**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 15**	**Day 21**	**Day 28**	**Day 34**	**Week 12**	**Week 24**	**ET (prior to Day 34)**	• Day relative to start of study intervention (Day 1). • Baseline (Day 1) visit is a mandatory visit. • Assessments indicated in brackets [X] are only to be conducted if indicated as described in the "Notes".
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	• Screening procedures may be done from Day -1 to Day 1 and may be completed on the same calendar day as Baseline/Day 1 procedures. If screening and baseline visits are conducted on the same calendar day, assessments and procedure that are listed to occur at both visits only need to be completed once.
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X			X	• AEs should be assessed by means of a telemedicine visit if an in-person visit is not feasible. • Previously identified AEs (either by interview, physical exam, or other assessment) should be monitored to the extent possible if telemedicine is used. • See Section 8.4.3 for follow-up AE and SAE assessments.

2. INTRODUCTION

Nirmatrelvir, a potent and selective SARS-CoV-2 3CL orally administered protease inhibitor, is being investigated in participants with rebound of COVID-19 symptoms and rapid antigen test positivity.

2.1. Study Rationale

Case reports in the literature describe individuals who have experienced symptomatic relapses of SARS-CoV-2 infection following completion of a 5-day course of nirmatrelvir/ritonavir[1-3]. In the available cases, patients are described as experiencing rapid improvement in systemic symptoms following initiation of treatment but then experience a rebound in COVID-19 symptoms after completing therapy. The time course of symptom rebound suggests that symptom recurrence is likely not related to re-exposure and that it does not reflect a potential re-infection event. In one case report, symptom relapse was accompanied by fluctuating RT-PCR cycle thresholds and antigen testing suggesting the potential for a rebound in viral replication. In a separate case series of 7 patients with recurrent symptoms, median SARS-CoV-2 RNA at baseline was 6.1 $\log_{10}$ copies/mL (range 4.2-7.3) and enrollment viral cultures were positive in 3 of 7 individuals[4]. Several of the published case reports on symptom recurrence included viral sequencing and these reports to date have not identified resistance mutations to nirmatrelvir.

A retrospective review of 483 high-risk patients treated with nirmatrelvir/ritonavir reported 4 (0.8%) of patients experienced rebound of symptoms. Median time to rebound was reported as 9 days. Rebound symptoms were characterized as mild and resolving without additional COVID-19 therapy with no patient requiring hospitalization[5].

Post-treatment increases in SARS-CoV-2 RNA levels (ie, viral RNA rebound) in nasopharyngeal samples were observed on Day 10 or Day 14 in a subset of nirmatrelvir/ritonavir and placebo recipients in the EPIC-HR study. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters but was generally similar among nirmatrelvir/ritonavir and placebo recipients, regardless of the rebound definition used. For participants who showed a half-$\log_{10}$ or greater increase relative to end of treatment and whose viral load was persistent through follow-up, the occurrence was 1.73% placebo and 2.32% nirmatrelvir/ritonavir. In addition to these, some participants had transient half-$\log_{10}$ or greater increases relative to end of treatment, the occurrence was 2.35% in placebo vs 4.65% nirmatrelvir/ritonavir. A similar or smaller percentage of placebo recipients compared to nirmatrelvir/ritonavir recipients had nasopharyngeal viral RNA results <LLOQ at all study timepoints in both the treatment and post-treatment periods. Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of nirmatrelvir/ritonavir treatment. Post-treatment viral RNA rebound also was not associated with drug resistance as measured by mPro sequencing. The clinical relevance of post-treatment increases in viral RNA following nirmatrelvir/ritonavir or placebo treatment is unknown.

At present, there are no controlled efficacy and safety data of a repeat 5-day course of nirmatrelvir/ritonavir in participants with acute rebound in symptoms and SARS-CoV-2

infection. Recurrence in symptoms along with a positive rapid antigen test following the completion of a 5-day course of nirmatrelvir/ritonavir may indicate that these patients require additional therapy to achieve sustained viral clearance. Such patients may benefit from an additional 5-day treatment duration. The purpose of this study is to evaluate the efficacy, safety and tolerability of a second 5-day treatment course of nirmatrelvir/ritonavir in participants with a rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks (14 days) following completion of an initial 5-day treatment course.

2.2. Background

COVID-19, caused by the SARS-CoV-2 coronavirus, was declared a global pandemic by the WHO on 11 March 2020[6], and continues to be a serious global threat to public health and to health care systems. As of 07 March 2022, COVID-19 has infected at least 446 million people, and has led to at least 6 million deaths worldwide[7].

In order to prevent SARS-CoV-2 infection, several COVID-19 vaccines have been approved or authorized for emergency use by Health Authorities and are being administered globally[8].

In December 2021, the FDA granted EUA for a 5 day course of treatment for 2 separate oral antiviral agents, nirmatrelvir/ritonavir[9] and molnupiravir[10], for the treatment of COVID-19 in adult and pediatric patients 12 years of age and older who weigh at least 40 kg, with mild to moderate COVID-19 who are at high risk for progressing to severe illness. In January 2022, remdesivir received approval for this same population[11]. This treatment is administered by IV infusion over 3 days for nonhospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe illness.

In this study of participants with rebound of COVID-19 symptoms and rapid antigen test positivity, nirmatrelvir/ritonavir will be administered for 5 days.

2.2.1. Clinical Overview

The safety and efficacy of a 5-day treatment with nirmatrelvir/ritonavir in adults was demonstrated in Study C4671005, which enrolled nonhospitalized symptomatic adults with laboratory-confirmed diagnosis of SARS-CoV-2 infection with at least 1 risk factor for progression to severe disease and with a COVID-19 symptom onset of ≤5 days. In the analysis of the primary endpoint from all participants enrolled in Study C4671005, an 89% reduction in COVID-19-related hospitalization or death from any cause compared with placebo in participants treated within 3 days of symptom onset was observed. 0.72% of participants who received nirmatrelvir/ritonavir were hospitalized through Day 28 following randomization (5 of 697 hospitalized with no deaths), compared to 6.45% of participants who received placebo and were hospitalized or died (44 of 682 hospitalized with 9 subsequent deaths) ($p<0.001$). In the final analysis of participants who initiated treatment ≤5 days from symptom onset and did not receive or were not expected to receive COVID-19 therapeutic mAbs treatment at time of randomization (mITT1 population), nirmatrelvir/ritonavir significantly reduced COVID-19–related hospitalization or death from 66/1046 (6.31%) to 9/1039 (0.87%) compared with placebo at Day 28 ($p<0.0001$), corresponding to an 86.3% relative risk reduction.

Refer to the IB[12] for more details on studies, including clinical efficacy, safety, and PK results for completed and ongoing studies.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Nirmatrelvir		
Emesis	In Study C4671005, vomiting occurred at a greater frequency in the nirmatrelvir/ritonavir group (1.1%) than in the placebo group (0.8%).	AEs will be monitored and participants may receive antiemetics if needed.
Hypertension	Transient increases in systolic, diastolic, and mean blood pressure were observed in the preclinical studies. In Study C4671005 (adults at high risk for severe disease), a small imbalance in hypertension AEs (1% vs <1%) was reported.	Vital signs and all AEs will be monitored in the study.
Reduced maternal and fetal weight	In rabbit embryo-fetal development toxicity studies, nirmatrelvir-related lower maternal body weight change and food consumption were observed at 1000 mg/kg/day but were not considered adverse based on low magnitude of difference from control and lack of impact on absolute body weights. Nirmatrelvir -related, adverse, lower fetal weight (0.91x control) was observed at 1000 mg/kg/day.	Lower dose of 300 mg q12h (or 150 mg q12h in moderate renal impairment) is used in this study.
Study Intervention(s) Ritonavir		
Gastrointestinal disturbances (including diarrhea, nausea, vomiting and abdominal pain)	Frequently reported adverse reaction in HIV positive patients who are HIV-positive at 600 mg BID.	Lower dose of 100 mg twice daily is used in this study. There will be close observation of AEs. Taking study intervention with food may improve tolerability.
Neurological disturbances (eg, paresthesia, including oral paresthesia, dysgeusia and dizziness)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs.
Rash (most commonly reported as erythematous and maculopapular, followed by pruritic)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs and monitoring through

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		targeted physical exams. If needed, therapeutic interventions per SoC may be provided.
Fatigue/Asthenia	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs.

2.3.2. Benefit Assessment

Nirmatrelvir/ritonavir has been shown to have SARS-CoV-2 antiviral activity in vitro. Efficacy, safety and tolerability of nirmatrelvir/ritonavir was demonstrated in adults at increased risk of progressing to severe COVID-19 illness. The EMA has granted marketing authorisation approval for nirmatrelvir/ritonavir for the treatment COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19[13]. The FDA has granted EUA for nirmatrelvir/ritonavir for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older and weighing ≥40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

2.3.3. Overall Benefit/Risk Conclusion

Considering the current COVID-19 global pandemic, the high burden of both mortality and morbidity, the potential for future epidemic outbreaks, the lack of readily available outpatient treatment options, and the measures taken to minimize risk to study participants, the potential risks identified in association with nirmatrelvir/ritonavir are justified by the anticipated benefits that may be afforded to participants with rebound of COVID-19 symptoms and rapid antigen test positivity. Rebound in symptoms along with a positive rapid antigen test following the completion of a 5-day course of nirmatrelvir/ritonavir may indicate that these patients may require additional therapy to achieve sustained viral clearance. Such patients may benefit from an additional 5-day treatment duration.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on viral RNA level in NP swabs in participants with mild-to-moderate COVID-19.	• The change in viral SARS-CoV-2 RNA level as measured in NP swabs from baseline to Day 5.	• The difference in mean change of SARS-CoV-2 RNA level in NP swabs from baseline to Day 5 between nirmatrelvir/ritonavir and placebo/ritonavir group in patients with a rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course ,who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on the duration of viral shedding.	• Time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2) h apart through Day 28.	• The hazard ratio for time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2) h apart through Day 28 between nirmatrelvir/ritonavir and placebo/ritonavir group in patients with rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on the duration and severity of signs and symptoms in participants with mild-to-moderate COVID-19.	• Time (days) to sustained alleviation of all targeted signs and symptoms through Day 28 where sustained alleviation is defined as the first of 2 consecutive days when any symptoms scored as moderate or severe at baseline are scored as mild or absent and any symptoms scored as mild or absent at baseline are scored as absent.	• The hazard ratio for time to sustained alleviation of all targeted signs and symptoms through Day 28 between nirmatrelvir/ritonavir and placebo/ritonavir group in patients with rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.
• To describe the safety and tolerability of nirmatrelvir/ritonavir in participants with mild-to-moderate COVID-19.	• Incidence of TEAEs. Incidence of SAEs and AEs leading to discontinuation.	• Not applicable.
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on viral RNA level in NP swabs in participants with mild-to-moderate COVID-19.	• Proportion of participants with SARS-CoV-2 RNA in NP swab below the LLOQ on Days 3, 5, 10, 15, 21, 28, and 34. • Proportion of participants with sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 log10 copies/mL) from Day 5 through Day 34. • Proportion of participants with SARS-CoV-2 RNA in NP swabs below the LLOQ (defined as <2.0 log10 copies/mL) on both Days 5 and 10. • The change in SARS-CoV-2 RNA level in NP swabs from baseline to Days 3, 10, 15, 21, 28, and 34. • Time to sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 log10 copies/mL) and	• Not applicable.

Objectives	Endpoints	Estimands
	remains below the LLOQ through Day 34 for participants with NP swab SARS-CoV-2 RNA greater than or equal to the LLOQ at baseline. • Rebound in SARS-CoV-2 RNA level in NP swabs at follow-up (ie, any study visit from Day 10 to through Day 34, defined as a half (0.5) $\log_{10}$ copies/mL increase or greater in SARS-CoV-2 RNA level relative to SARS-CoV-2 RNA level on Day 5 and with a follow-up viral RNA level $\geq$2.5 $\log_{10}$ copies/mL.	
• To compare the effect of nirmatrelvir/ritonavir on the rate of cell culture infectious virus over time in participants with mild-to-moderate COVID-19	In participants with detectable viral titers at baseline by TCID50: • Time to negative infectious titer by TCID50. • Change in TCID50 from baseline to Days 3, 5, 10, 15, 21, 28, and 34. • Proportion of participants with negative infectious titer by TCID50 on Days 3, 5, 10, 15, 21, 28, and 34. In participants with positive viral titers at baseline by virus recovery: • Time to negative infectious titer by virus recovery. • Proportion of participants with negative infectious titer by virus recovery on Days 3, 5, 10, 15, 21, 28, and 34.	• Not applicable
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on viral concentration in plasma in participants with mild-to-moderate COVID-19.	• Change from baseline in SARS-CoV-2 viral RNA level in plasma, over time.	• Not applicable.
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on COVID-19-related hospitalization and all-cause mortality in participants with mild-to-moderate COVID-19.	• Proportion of participants with COVID-19-related hospitalization >24 h or death from any cause through Day 28.	• Not applicable.
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on COVID-19-related healthcare resource utilization in participants with mild-to-moderate COVID-19.	• Number of COVID-19-related medical visits through Day 34.	• Not applicable.
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on the duration and severity of signs and symptoms in participants with mild-to-moderate COVID-19.	• Time (days) to sustained resolution of all targeted signs and symptoms through Day 28 where sustained resolution is defined as the first of two consecutive days when all targeted COVID-19 symptoms are scored as absent.	• Not applicable

4. STUDY DESIGN

4.1. Overall Design

This Phase 2, randomized, double-blind, placebo-controlled study will evaluate the efficacy and safety of a repeat 5-day treatment course of nirmatrelvir/ritonavir or placebo/ritonavir for the treatment of mild-to-moderate COVID-19. Participants must have written documentation, such as an electronic health record, medical record, or prescription receipt of treatment with nirmatrelvir/ritonavir (verbal assertion of treatment is not acceptable) with patient-reported 100% compliance (ie, completed a 5 day course of nirmatrelvir/ritonavir). They must have experienced alleviation or resolution in COVID-19 signs/symptoms followed by a worsening (rebound) of signs/symptoms along with a positive rapid antigen test **after** completing an initial 5-day course of nirmatrelvir/ritonavir. The onset of rebound in COVID-19 symptoms along with evidence of SARS-CoV-2 infection must occur within 2 weeks (14 days) **after** completion of an initial 5-day course of nirmatrelvir/ritonavir.

Eligible participants for this study will be randomly assigned (2:1 allocation of active to placebo) to receive:

- nirmatrelvir plus ritonavir orally q12h for 5 days; or
- placebo plus ritonavir orally q12h for 5 days.

Randomization will be stratified by geographic region.

Participants will be screened within 24 hours before randomization.

Participants must be randomized within 48 hours from the onset of the rebound COVID-19 symptoms and must be randomized within 24 hours of a positive baseline rapid antigen test. The total study duration is up to 24 weeks, including study intervention administration through Day 5 or Day 6, efficacy and safety assessments through Day 34, and long-term follow up at Weeks 12 and 24.

Participants are eligible if they are at least 12 years of age (and weigh ≥40 kg at screening) and have at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19. However, participants who are immunocompromised are excluded from this study as they may have prolonged viral shedding due to their immunocompromised state[14,15]. Participants will be eligible for enrollment irrespective of COVID-19 vaccination/boosted status (except for time course restrictions listed in the exclusion criteria).

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

The primary analysis will be performed after all participants have completed the Day 34 visit. The follow-up analysis will be performed after all participants have completed the Week 24 visit.

4.2. Scientific Rationale for Study Design

Case reports in the literature describe individuals who have experienced symptomatic relapses of SARS-CoV-2 infection following completion of a 5-day course of nirmatrelvir/ritonavir[1-3]. In the available cases, patients are described as experiencing rapid improvement in systemic symptoms following initiation of treatment but then experience a rebound in COVID-19 symptoms after completing therapy. The time course of symptom rebound suggests that symptom recurrence is likely not related to re-exposure and it does not reflect a potential re-infection event.

In Study C4671005 (EPIC-HR; NCT04960202), post-treatment increases in SARS-CoV-2 RNA shedding levels (ie, viral RNA rebound) in nasopharyngeal samples were observed on Day 10 and/or Day 14 in a subset of nirmatrelvir/ritonavir and placebo recipients, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters but was generally similar among nirmatrelvir/ritonavir and placebo recipients, regardless of the rebound definition used. A similar or smaller percentage of placebo recipients compared to nirmatrelvir/ritonavir recipients had nasopharyngeal viral RNA results <LLOQ at all study timepoints in both the treatment and post-treatment periods[9].

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of nirmatrelvir/ritonavir treatment. Post-treatment viral RNA rebound also was not associated with drug resistance as measured by Mpro sequencing. The clinical relevance of post-treatment increases in viral RNA following nirmatrelvir or placebo treatment is unknown[9].

At present, there are no controlled efficacy and safety data of a repeat 5-day course of nirmatrelvir/ritonavir in participants with acute rebound in symptoms and SARS-CoV-2 infection. Rapid rebound in symptoms along with a positive rapid antigen test following the completion of a 5-day course of nirmatrelvir/ritonavir may indicate that these patients require additional therapy to achieve sustained viral clearance. Such patients may benefit from an additional 5-day treatment duration. The purpose of this study is to evaluate the efficacy, safety and tolerability of a second 5-day treatment course of nirmatrelvir/ritonavir in participants with a rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course that a participant received as part of routine clinical care.

A 2-week time-period for rebound symptoms and SARS-CoV-2 infection was selected to enroll a population that has a presumptive recurrence of the same viral illness and not a new SARS-CoV-2 infection. Symptom burden including alleviation, resolution and worsening (rebound) to qualify for the study is based on the judgment of **both** the participant along with investigator judgment.

In order to avoid potential unblinding given the characteristic taste disturbance AEs associated with ritonavir, all participants in this study will receive ritonavir and be randomly assigned to either nirmatrelvir or placebo. 100 mg ritonavir will be administered in the nirmatrelvir placebo group to match the 100 mg ritonavir in the active treatment group.

Ritonavir is an inhibitor of CYP3A4 and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A4. In order to avoid potential unblinding due to the magnitude of drug-drug interactions, all participants in this trial will receive ritonavir, and be randomly assigned to either nirmatrelvir or placebo.

4.2.1. Choice of Contraception/Barrier Requirements

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

4.2.3. Inclusion of Pediatric Participants

This study includes participants of 12 years of age and older and weighing ≥40 kg, which is consistent with the Fact Sheet for nirmatrelvir/ritonavir where FDA has granted EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older and weighing ≥40 kg)[16].

4.3. Justification for Dose

On 22 December 2021, the US FDA granted EUA to nirmatrelvir/ritonavir for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kg) who are at risk for progression to severe disease. The recommended dose is 300 mg nirmatrelvir co-administered with 100 mg ritonavir q12h for 5 days for subjects with normal renal function or mild renal impairment. This dose was well tolerated in Study C4671005 and reduced the rate of hospitalization or death by 89% compared with placebo in symptomatic adult participants with COVID-19 who were at increased risk of progression to severe disease.

Results from the renal impairment study showed that the adjusted geometric mean (90% CI) test/reference ratios comparing moderate renal impairment (test) to normal renal function (reference) for nirmatrelvir AUC_{inf} and C_{max} was 187.40% (148.52%, 236.46) and 138.12% (113.18%, 168.55%), respectively. Due to the increase in in exposures of nirmatrelvir in those with moderate renal impairment, and verified by modeling and simulation, the nirmatrelvir/ritonavir dose in patients with moderate renal impairment was reduced to 150 mg/100 mg q12h.

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants aged 12 years or older and weighing ≥40 kg at screening (Section 10.10.1).

    - Refer to Appendix 4 for reproductive criteria for female (Section 10.4.1) participants.

Disease Characteristics:

2. Participants must have written documentation with patient-reported 100% compliance (ie, completed a 5 day course of nirmatrelvir/ritonavir). They must have symptom alleviation or resolution in COVID-19 signs/symptoms followed by a worsening (rebound) of signs/symptoms after completing an initial 5-day course of nirmatrelvir/ritonavir based on the judgement of both the participant and investigator (Section 10.10.2).

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

4. Onset of rebound in signs/symptoms attributable to COVID-19 within 48 hours prior to randomization and ≥1 sign/symptom attributable to COVID-19 present on the day of randomization (Section 10.10.2).

5. SARS-CoV-2 infection as determined by rapid antigen testing in any specimen collected within 24 hours prior to randomization and collected within 2 weeks (14 days) after the completion of the initial 5-day treatment course of nirmatrelvir/ritonavir.

6. Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (Section 10.10.4).

5.2. Exclusion Criteria

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

Medical Conditions:

1. Current need for hospitalization, hospitalized for the index COVID-19 infection, or anticipated need for hospitalization within 24 h after randomization in the clinical opinion of the site investigator.

2. History of severe chronic liver disease (eg, jaundice, ascites, hepatic encephalopathy, history of bleeding esophageal or gastric varices). No laboratory testing is needed.

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

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

5. Receiving dialysis or eGFR <30 mL/min/1.73 m^2 (for adults) or eCrCl <30 mL/min (for adolescents) at screening using creatinine point of care device (see Section 10.7.1 for age-specific kidney function calculation).

6. Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization (Section 10.10.4).

7. Immunocompromised (Section 10.10.7).

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

Prior/Concomitant Therapy:

9. Current use of any prohibited concomitant medication(s) (see Section 6.9; Appendix 8, and Section 10.10.6).

10. COVID-19 vaccination within 14 days prior to study entry or anticipated COVID-19 vaccination through Day 34.

11. Receiving other COVID-19 specific treatments within 30 days of randomization and through Day 34, excluding a single 5-day treatment course of nirmatrelvir/ritonavir as well as blinded study medication (Section 10.10.6).

Prior/Concurrent Clinical Study Experience:

12. Prior participation in this trial.

13. Current or previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Other Exclusion Criteria:

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

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

5.3. Lifestyle Considerations

5.3.1. Contraception

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

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

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Section 10.4.3) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

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

5.4. Screen Failures

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

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

To assist in further understanding rebound, the following screen failure information will be captured in the eCRF and included in the study report.

- Number (%) of participants with rebound symptoms at time of screening but who are negative by rapid antigen testing at screening and therefore screen fail for the study.

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

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

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

6.1. Study Intervention(s) Administered

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

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

Study Intervention(s)			
Intervention Name	Nirmatrelvir	Placebo for nirmatrelvir	Ritonavir
Arm Name (group of participants receiving a specific	nirmatrelvir/ritonavir	placebo	ritonavir

Study Intervention(s)			
treatment or no treatment)			
Type	drug	placebo	drug
Dose Formulation	tablet	tablet	capsule
Unit Dose Strength(s)	150 mg	0 mg	100 mg
Dosage Level(s)	300 mg q12h for 5 days 150 mg q12h for 5 days (for participants with eGFR ≥30 to <60 mL/min/1.73 m^2 (or eCrCl ≥30 to <60 mL/min) at screening)	0 mg q12h for 5 days	100 mg q12h for 5 days
Route of Administration	Oral	Oral	Oral
Use	Experimental	Placebo	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IPM.	Provided centrally by the sponsor. Refer to the IPM.	Provided centrally by the sponsor. Refer to the IPM.
Packaging and Labeling	Study intervention will be provided in blister wallets. Each wallet will be labeled as required per country requirement. Products will be provided with blinded labels.	Study intervention will be provided in blister wallets. Each wallet will be labeled as required per country requirement. Products will be provided with blinded labels.	Study intervention will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement. Products will be provided with open labels.
Current/Former Name(s) or Alias(es)	PF-07321332	NA	ritonavir

Study Arm(s)		
Arm Title	Nirmatrelvir/ritonavir	Placebo/ritonavir
Arm Type	Experimental	Other
Arm Description	Participants will receive nirmatrelvir/ritonavir 300 mg/100 mg (or 150 mg/100 mg for participants with	Participants will receive placebo 0 mg/ritonavir 100 mg q12h for 5 days.

	eGFR ≥30 to <60 mL/min/1.73 m^2 or eCrCl ≥30 to <60 mL/min) q12h from Day 1 through Day 5.	
Associated Intervention Labels	Nirmatrelvir/ritonavir	Placebo/ritonavir

6.1.1. Administration

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

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

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

Participants should take the first dose of study intervention on Day 1, during the in-person visit; that is, participants should take nirmatrelvir/placebo and ritonavir at the same time (no more than 15 minutes apart). The study intervention should be taken every 12 hours (±4 hours), and not more than twice in a calendar day. Depending on the time of first dose, the timing of the second dose may be adjusted slightly to allow the participant/caregiver to select a convenient 12 hour dosing schedule as long as the next dose is taken at least 4 hours, but no later than 16 hours, after the first dose. Once the dosing schedule is adjusted, all subsequent doses should be taken every 12 hours (±4 hours).

If a dose is delayed, it should be taken as soon as possible (but no later than 8 hours after the scheduled 12-hourly dose time), then resume the normal dosing schedule. If the participant misses a dose by more than 8 hours, the participant should not take the missed dose and instead take the next dose at the regularly scheduled time. The participant should not double the dose to make up for a missed dose. Dosing should be stopped at the end of the treatment period (Day 5 or 6). Any remaining tablets and/or capsules at the Day 5 visit should be returned. If the Day 5 visit is conducted prior to the last dose of study intervention (ie. Day 6), any remaining tablets or capsules should be collected at the next visit.

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

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

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

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

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention containers that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. **Returned study intervention must not be redispensed to the participants.**

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. If destruction is

authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

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

6.2.1. Preparation and Dispensing

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

6.3. Assignment to Study Intervention

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

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

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

6.4. Blinding

This is a double-blind study.

6.4.1. Blinding of Participants

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

6.4.2. Blinding of Site Personnel

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

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

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

6.4.3. Blinding of the Sponsor

Sponsor staff will be blinded to participants' assigned study intervention, except for designated individuals who may conduct unblinded reviews of the data if requested by regulatory authorities. An unblinded submissions team may be assembled to prepare unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing.

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

The study will be unblinded after all participants complete the Day 34 visit (or ET prior to Day 34 visit) and analyses through Day 34, including the primary efficacy endpoint analyses, will be conducted.

Details of the unblinded sponsor staff supporting the data review(s) described above and the timing of unblinding will be outlined in the Unblinding Plan.

6.4.4. Breaking the Blind

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

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

6.5. Study Intervention Compliance

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

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

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

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

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

The following noncompliance cases will be considered medication errors (see Section 6.5):

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

In addition to the above listed-medication errors, any deviation from protocol-specified dosing (eg, missed single dose or partial dose) should be recorded as a protocol deviation and the investigator or designee is to counsel the participant/guardian and ensure steps are taken to improve compliance.

6.6. Dose Modification

Not applicable.

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

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

6.8. Treatment of Overdose

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

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

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

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

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

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

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

6.9. Prior and Concomitant Therapy

Permitted During the Study

Concomitant medications are permitted unless specifically listed as prohibited medication (see Appendix 8) or as defined in Section 5.2. However, as described below, use of other specific COVID-19 treatments (eg, antivirals or monoclonal antibodies) are prohibited during the study.

Sites should consult with the sponsor if a new SoC option for COVID-19 becomes available after study initiation. The Investigator should ensure that any concomitant therapy is not a strong inducer of CYP3A4 or highly dependent on CYP3A4 for clearance. The Pfizer medical monitor should be consulted to review for potential drug-drug interactions (see Appendix 8).

Ritonavir is an inhibitor of CYP3A4 and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A4. Participants will receive ritonavir for 5 days but as treatment is blinded, some concomitant medications (Appendix 8, Table 4) may require monitoring of drug levels, consideration of temporary withdrawal of the concomitant medication, or dose adjustment throughout the study treatment period and following completion of the blinded treatment duration period.

Prohibited During the Study

Participants are prohibited from receiving a non-study COVID-19 antiviral or monoclonal antibody therapy for COVID-19 within 14 days prior to randomization (excluding qualifying treatment with nirmatrelvir/ritonavir) and through completion of Day 34. Vaccination for COVID-19 is also prohibited within 14 days prior to randomization and through completion of Day 34.

As an exception, participants who progress to severe or critical COVID-19 will, however, be permitted to receive specific COVID-19 treatment(s) such as antiviral therapy or use of other treatments considered standard of care and the above restriction would not apply.

Nirmatrelvir and ritonavir are both primarily metabolized by CYP3A4. In addition, ritonavir is a strong inhibitor of CYP3A4. Therefore, concomitant use of medications that are strong

inducers of CYP3A4 and which are contraindicated in combination with nirmatrelvir/ritonavir (see Appendix 8 Table 3) are prohibited during study treatment. Some medications that are highly dependent on CYP3A4 for clearance are also contraindicated with nirmatrelvir/ritonavir (see Appendix 8, Table 3).

Some other medications that are not contraindicated but are highly dependent on CYP3A4 for clearance may require dose adjustment or additional monitoring. Refer to Appendix 8 Table 4 for a nonexhaustive list of these medications and consult the Pfizer medical monitor for guidance on coadministration with nirmatrelvir/ritonavir.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- AE of Grade 3 severity or greater and considered by the investigator to be related to study intervention;
- SAE considered by the investigator to be related to study intervention;
- Requirement for prohibited concomitant medication;
- Study terminated by sponsor;
- Withdrawal by participant or legally authorized representative;
- If postscreening eGFR is <30 mL/min/1.73 m^2 (adult participants) or eCrCl is <30 mL/min (adolescent participants), the participant will be instructed to discontinue any remaining study intervention doses as soon as study staff become aware of the eGFR results.

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

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for all subsequent scheduled assessments. See the SoA for data to be

collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

7.1.1. Pregnancy

For further details, refer to Section 8.4.5.1.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

At the time of discontinuing from the study (if prior to Day 34), if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

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

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent/assent for any further

contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

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

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

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

- In the event the participant is deemed unreachable, the investigator should utilize the contact information collected for the 2 individuals who can be contacted if the participant cannot be reached after multiple attempts.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

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

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

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

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

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

In the event a participant is hospitalized, study assessments should be performed as feasible. Procedures not performed due to hospitalizations will not be considered protocol deviations.

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

8.1.1. Baseline Procedures

8.1.1.1. Medical History

Medical history, COVID-19 disease history and SARS-CoV-2 tests results if available, and demographics will be collected at screening. Smoking status will be collected. Complete medication history of all prescription or nonprescription drugs (including vaccinations), and dietary and herbal supplements taken within 30 days prior to the planned first dose will be collected. COVID-19 vaccinations, antiviral and monoclonal antibody treatment for the treatment of COVID-19 at any time prior to the planned first dose will also be collected.

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

8.1.1.2. Secondary Contacts

At baseline and as noted in the SoA, the investigator will collect contact information for at least 2 individuals who can be contacted if the participant cannot be reached after multiple attempts. Secondary contacts may be used to determine if a participant is lost to follow-up or vital status check.

8.1.2. Household Characteristics

Household characteristics will be determined through interview with the study participant and will be updated during the study. The household characteristics include:

- Number of people living in household;
- Number of additional confirmed SARS-CoV-2 positive or suspected (ie, symptomatic) household members and date of confirmed or suspected SARS-CoV-2.

8.1.3. Telehealth Visits

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

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

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

Observe (ie, video, videoconferencing software) the participant performing the rapid antigen test (participant self collected rapid antigen test), if the procedure is conducted remotely, and record the results for offsite visits in accordance with the SoA.

8.1.4. Home Health Visits

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

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.

- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Collect clinical laboratory and biomarker samples.
- Observe rapid antigen testing, record result, and collect NP/OP swab samples.
- Collect vital signs.
- Confirm the participant has completed the PRO assessments.
- Retrieve unused study intervention and empty study intervention containers
- Collect/update secondary contacts
- Collect/update household characteristics
- Collect COVID-19-related medical visits
- Collect COVID-19 adjunctive therapeutic procedures
- If the HCP is unable to collect AEs, concomitant medications, the site should contact the participant via a follow-up telephone call to collect the additional information.

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

8.2. Efficacy Assessments

8.2.1. Participant Diary

Participants will be provided an electronic handheld device or will use their own device to record study intervention administration, signs and symptoms of COVID-19, and PRO assessments in the study diary.

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

The diary allows recording of these assessments only within a fixed time window (next calendar day), thus providing an accurate representation of the participant's experience at that time. The participant is able to make revisions to incorrect entries before pressing the save or submit button. In the event that a participant becomes aware of an error in data after the entry is saved, a change to the diary data may only be made by the investigator submitting a data clarification form. Data reported in the participant diary will be transferred

electronically to a third-party vendor, where they will be available for review by investigators and the sponsor or delegate at all times via an internet-based portal.

8.2.2. COVID-19-Related Medical Details

Details of participants' COVID-19-related medical visits will be collected. These are hospitalization of any duration, urgent care, emergency room ≤24h, practitioner's office, telemedicine, home health care services or extended care facility stay and will be collected during study visits, including level of care (ICU status) and dates of utilization, including admission and discharge, as applicable.

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

8.2.3. PRO Assessments

PRO assessments will be recorded in the study eDiary.

8.2.3.1. Global Impression Questions

Three questions will be included in the ePRO to assess patient-reported global impression items: a) return to usual health; b) return to usual activities; and c) overall COVID-19-related symptoms[17]. For participants who report COVID-19 symptoms in the diary, the global impression questions will be answered after the completion of the COVID-19 signs and symptoms diary is completed.

8.2.3.2. SF-36 v2® Health Survey (Acute Form)[18]

Only adult study participants ≥18 years of age at the time of screening will be asked to complete the SF-36 at the timepoints indicated in the SoA.

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

8.2.3.3. WPAI

Only adult study participants ≥18 years of age at the time of screening will be asked to complete the WPAI at the timepoints indicated in the SoA.

COVID-19 impacts manual and office-based work, and results in missed work due to illness or quarantine and loss of productivity [19]. The WPAI-GH is being implemented for COVID 19 (ie, WPAI-COVID-19) in order to evaluate change from baseline in work burdens. The WPAI-GH has demonstrated validity, reliability and sufficient predictive value to measure the impact of disease on absenteeism, presenteeism, and overall productivity in a manner that can also be monetized [20].

The WPAI-COVID-19 consists of 6 questions that refer to the following assessments for work productivity: 1 = currently employed, 2 = hours missed due to health problems, 3 = hours missed for other reasons, 4 = hours actually worked, 5 = degree health affected productivity while working (using a 0 to 10 VAS), and 6 = degree health affected productivity in regular unpaid activities. The recall period for questions 2 through 6 is 7 days. Four main outcomes will be generated from the WPAI-COVID-19 and reported as: 1) percent work time missed due to COVID-19 for those who are currently employed, 2) percent impairment while working due to COVID-19 for those who are currently employed and actually worked in the past 7 days, 3) percent overall work impairment due to COVID-19 for those who are currently employed, and 4) percent activity impairment due to COVID-19 for all respondents [20]. The WPAI-COVID-19 will be completed as specified in the SoA.

8.2.3.4. EQ-5D-5L Scale

Only adult study participants ≥18 years of age at the time of screening will be asked to complete the EQ-5D-5L at the timepoints indicated in the SoA.

The EQ-5D is a validated, standardized, generic instrument that is a preference-based health related quality of life questionnaire in cost effectiveness and HTA[21-23]. Recently, a version was developed called EQ-5D-5L with 5 response levels on each dimension compared to the 3 response levels in the EQ-5D-3L[21-27].

Measurement properties of the EQ-5D-5L demonstrated to be a valid version of the 3 level questionnaire that improved measurements by adding discriminatory power, reducing the ceiling, and establishing convergent and known groups validity[21,23,25,26]. Both the EuroQol EQ-5D-3L and EQ-5D-5L versions are well established instruments used to measure health states and utilities in various diseases areas and assess mobility, self-care, usual activities, pain/discomfort, anxiety/depression and health status using a VAS[24,28]. The EQ-5D-5L should be completed as described in the SoA.

8.2.3.5. COVID-19 Signs and Symptoms

On Day 1, participants will complete the COVID-19 signs and symptoms (Appendix 11) in the study diary, before receiving study intervention. Participant assessment of COVID-19-related symptoms should be recorded at approximately the same time each day as specified in the SoA and as described in Appendix 11.

COVID-19-related symptoms will be evaluated in accordance with FDA guidelines. Participants will record a rating of their symptom severity over the past 24 hours based on a 4-point scale in which 0 is reported if no symptoms were present; 1 if mild; 2 if moderate; and 3 if severe.

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

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

During the long-term follow-up period as noted in the SoA, site staff will ask participants if they have experienced pre-defined COVID-19 signs and symptoms or other symptoms believed to be related to COVID-19, over the past 7 days, including the day of the study visit. For each sign or symptom reported, the worst severity (mild, moderate or severe) during the past week should be recorded in the CRF.

8.3. Safety Assessments

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

8.3.1. Targeted Physical Examination, Height and Weight

Physical examination is to be completed before administration of study intervention.

A targeted physical examination will include, at a minimum, cardiopulmonary assessments. Height and weight will also be measured and recorded at screening, though height may be self-reported for participants ≥18 years of age.

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

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

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.

8.3.2.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with the participant, preferably in the seated position with their feet on the floor when possible with a completely automated device[29]. It is recommended that the same position should be used for a participant throughout the study duration. Manual techniques will be used only if an automated device is not available.

8.3.2.2. Temperature and Respiratory Rate

Temperature and respiratory rate will be assessed.

8.3.2.3. Oxygen Saturation Level

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

8.3.2.4. Point-of-Care Serum Creatinine Assessments

A serum creatinine point-of-care device will be used to assess kidney function as described in the SoA and Appendix 7. If a serum creatinine point-of-care device assessment is performed at screening and baseline, the baseline estimate of kidney function will determine eligibility.

8.3.3. Clinical Safety Laboratory Assessments

Laboratory safety parameters will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events[30], version 2.1. See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

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

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

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

8.3.3.1. Alternative Facilities for Clinical Safety Laboratory Assessment

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant’s source

documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

8.3.4. Pregnancy Testing

A serum or urine pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at Day 34 or the ET visit. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

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

8.3.4.1. At Home Pregnancy Testing

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

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

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion then inseminates his female partner prior to or around the time of conception.

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

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

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed PSSA case 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 using PSSA. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

that she is breastfeeding after having been exposed to the study intervention by ingestion.

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.
- The administration of study intervention consistent with the medication error descriptions in Section 6.5.

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

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

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

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 Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

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

8.7. Biomarkers

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

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

- Nasopharyngeal swab will be collected to assess SARS-CoV-2 viral RNA level.
- A plasma sample will be collected to assess SARS-CoV-2 viral RNA level.
- Oropharyngeal swab will be collected to assess SARS-CoV-2 viral RNA level
- A plasma sample will be collected and may be used for protein biomarker analysis.
- Retained research samples.

8.7.1. Viral RNA Assessment (NP Swab)

An NP swab of both nares will be collected by HCP as per the SoA from participants and will be analyzed to measure SARS-CoV-2 RNA by RT-PCR. At Screening and Baseline (Day 1) only, rapid antigen testing can be done before NP swab collection. At all other timepoints, **NP swab collection must occur prior to any Rapid Antigen Assessment**. Residual samples may be used for viral sequencing to assess for signs of viral evolution and evaluation of potential genetic viral variants, infectivity, phenotypic assays, and additional molecular analysis. Host genetic analysis may also be performed.

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

8.7.2. Viral RNA Assessment (Plasma)

A 6-mL blood sample will be collected per the SoA from participants and may be analyzed to measure SARS-CoV-2 RNA by RT-PCR. Residual samples may be utilized for viral sequencing, infectivity and phenotypic assays and additional molecular analysis. Host genetic analysis may also be performed.

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

8.7.3. Rapid Antigen Assessments

Rapid antigen testing for SARS-CoV-2 will be self-collected by the participant as described in the SoA. Sites will use test kits that are authorized for use in this study. At Screening and Baseline (Day 1) only, rapid antigen testing can be done before NP swab collection. At all other time points, rapid antigen testing must be done after NP swab collection. When participants have 2 consecutive negative rapid antigen tests separated by at least 24[-2]h, rapid antigen testing will revert to on site rapid antigen testing as noted in the SoA.

Site staff should train participants/caregiver at the screening/baseline visit to ensure participants can perform the rapid antigen test appropriately. The participant should perform the baseline rapid antigen testing assessment during the visit to ensure proper sample collection under observation by site staff.

8.7.4. Viral Sequencing Assessments (OP Swab)

An OP swab will be collected by the HCP as per the SoA from participants may be analyzed to measure SARS-CoV-2 RNA by RT-PCR. **OP swabs should be obtained after NP swab collection and rapid antigen testing**. Residual samples may be utilized for viral sequencing, infectivity and phenotypic assays and additional molecular analysis. Host genetic analysis may also be performed.

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

8.7.5. Specified Gene Expression (RNA) Research

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

8.7.6. Specified Protein Research

8.7.6.1. Plasma for Protein Analysis

A 6-mL blood sample will be collected, as specified in the SoA, and isolated for plasma for biomarker analysis. Analysis may include but is not limited to proteomics and immunologic assessments. Residuals of all samples may be stored and used for additional analyses related to COVID-19 and/or the mechanism of action of nirmatrelvir/ritonavir.

Details on processes for collection and shipment of these sample(s) can be found in the laboratory manual.

8.7.7. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.8. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

- 4-mL whole blood Prep B2.5 optimized for serum
- 2.5-mL whole blood Prep R1 optimized for RNA;
- 15-mL urine Prep M3.

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

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

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters will be evaluated in this study (Section 8.2.2 and Section 8.2.3).

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 Hypothesis

The primary hypothesis is to test whether or not there is a difference in mean change of viral RNA level in NP swabs from baseline to Day 5 between nirmatrelvir/ritonavir and the placebo/ritonavir group:

Null hypothesis: H_0 $\mu_{\text{nirmatrelvir/ritonavir}} - \mu_{placebo/ritonavir} = 0$

Alternative hypothesis: H_a $\mu_{\text{nirmatrelvir/ritonavir}} - \mu_{placebo/ritonavir} \neq 0$

Where $\mu_{\text{nirmatrelvir/ritonavir}}$ and $\mu_{\text{placebo/ritonavir}}$ are mean change of viral RNA level in NP swabs from baseline to Day 5 for nirmatrelvir/ritonavir and placebo/ritonavir groups.

9.1.1. Estimands

9.1.1.1. Primary Estimand

The primary estimand is the difference in mean change of SARS-CoV-2 RNA level in NP swabs from baseline to Day 5 between nirmatrelvir/ritonavir and placebo/ritonavir group in patients with a rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.

9.1.1.2. Secondary Estimands

The secondary estimands are:

- The hazard ratio for time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2) h apart through Day 28 between nirmatrelvir/ritonavir and placebo/ritonavir group in patients with rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.

- The hazard ratio for time to sustained alleviation of all targeted signs and symptoms through Day 28 between nirmatrelvir/ritonavir and placebo/ritonavir group in patients with rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.

9.1.2. Multiplicity Adjustment

The overall Type I error rate across the primary and key secondary efficacy endpoints will be controlled at alpha = 0.05. Following the positive test of the primary efficacy endpoint in the primary analysis set (mITT), the secondary analysis for the primary efficacy endpoint using the mITT1 analysis set will be tested.

Following the positive test of the secondary analysis, the following secondary efficacy endpoints will be tested using Hochberg method[31]:

- Time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2)h apart through Day 28 in the mITT analysis set.

- Time (days) to sustained alleviation of all targeted signs and symptoms through Day 28 where sustained alleviation is defined as the first of two consecutive days when any symptoms scored as moderate or severe at baseline are scored as mild or absent and any symptoms scored as mild or absent at baseline are scored as absent in the mITT analysis set.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Full analysis set (FAS)	All participants randomly assigned to study intervention.
Safety analysis set (SAS)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they received.
mITT	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and who have a positive viral RNA NP swab test result ($\geq$2.0 $\log_{10}$ copies/mL) at baseline. Participants will be analyzed according to the study intervention they were randomized.
mITT1	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and who have a positive rapid antigen test result at baseline. Participants will be analyzed according to the study intervention they were randomized.
Per protocol(PP)	All participants in the mITT analysis set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint. Protocol deviations will be reviewed to generate the list of participants with significant deviations to be excluded from the PP analysis set. The PP exclusion criteria will be finalized prior to breaking the blind.

9.3. Statistical Analyses

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

9.3.1. General Considerations

Baseline demographic and other characteristics will be tabulated for the FAS and summarized by treatment group. Quantitative variables will be described by standard descriptive statistics and qualitative variables will be summarized by frequency tables with number and proportion in each category.

For continuous endpoints, an MMRM or ANCOVA model will be used to analyze change from baseline, whichever is appropriate. Estimated mean differences between treatments groups will be calculated.

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

For count endpoints, the total number of the events and average number of events will be summarized for each group.

Time to event will be summarized graphically using Kaplan-Meier plots for each treatment group. Treatment comparisons will be conducted using log-rank test or Cox proportional hazard model as appropriate.

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

9.3.2.1. Definition of Endpoint(s)

The primary efficacy endpoint is the change in viral SARS-CoV-2 RNA level from baseline to Day 5 as measured in NP swabs.

9.3.2.2. Main Analytical Approach

The primary analysis for mean change in SARS-CoV-2 RNA level from baseline will be performed using a MMRM. The analysis will include the fixed effects of treatment, geographic region, baseline viral RNA level, visit, and treatment-by-visit interaction. An unstructured (co)variance structure will be used to model the within-participant variability. The LS means and treatment difference for each visit will be calculated and presented with their corresponding 95% CIs. The primary comparison for treatment effect will be the difference in LS means and 95% CI at Day 5. The primary analysis will be performed using mITT analysis set.

The secondary analysis for primary endpoint will be performed using the mITT1 analysis set.

9.3.3. Secondary Endpoints

9.3.3.1. Time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart through Day 28

For the event of 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart through Day 28, the date of the first negative rapid antigen test result will be considered the First Event Date.

Time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart for the purpose of this study is defined as:

- For a participant achieving the event, time to event will be calculated as (First Event Date) – (First Dose Date) +1.
- For a participant not achieving the event (censored), censoring date will be at the last date of rapid antigen test measurement, and time will be calculated as (Censoring Date) – (First Dose Date) +1 or Day 27 whichever occurs first (Day 27 is the last

possible day to achieve 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart through Day 28).

Cox proportional hazard model analyses will be used for time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart in mITT analysis set. Cox proportional hazard model will include treatment, geographic region and potential covariates as appropriate. The treatment group comparison will be presented as the estimate of the hazard ratio, 95% CI and p-value. In addition, time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart will be summarized graphically using Kaplan-Meier plots for each of the treatment groups in mITT analysis set.

Similar analyses for time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart will also be performed in the mITT1 analysis set.

9.3.3.2. Time (days) to sustained alleviation of all targeted signs and symptoms through Day 28

Sustained alleviation of all targeted COVID-19 signs/symptoms is defined as the event occurring on the first of 2 consecutive days when all symptoms scored as moderate or severe at study entry are scored as mild or absent AND all symptoms scored mild or absent at study entry are scored as absent. The first day of the 2 consecutive-day period will be considered the First Event Date.

For symptoms with no reported severity in baseline, the symptom will have to be absent in order to be counted as sustained alleviated (missing severity at baseline will be treated as mild).

Day 27 is the last possible day that symptom alleviation can be achieved (definition includes data from the subsequent day) and Day 28 is the last day participants report their daily signs and symptoms.

The time to sustained symptom alleviation for the purpose of this study is defined as:

- For a participant with sustained symptom alleviation, time to event will be calculated as (First Event Date) – (First Dose Date) +1.
- For a participant that either completes Day 28 of the study or discontinues from the study before Day 28 without sustained symptom alleviation(censored), censoring date will be at the last date on which symptom alleviation is assessed, and time will be calculated as (Censoring Date) – (First Dose Date) +1 or Day 27 whichever occurs first.

Participants who are hospitalized for the treatment of COVID-19 or die from any cause during the 28-day period will be classified as not achieving sustained symptom alleviation and will be censored at day 27.

Cox proportional hazard model analyses will be used for time to sustained symptom alleviation in mITT analysis set. Cox proportional hazard model will include treatment, geographic region and potential covariates as appropriate. The treatment group comparison

will be presented as the estimate of the hazard ratio, 95% CI and p-value. In addition, time to sustained symptom alleviation will be summarized graphically using Kaplan-Meier plots for each of the treatment groups in mITT analysis set.

Similar analyses for time to sustained symptom alleviation will also be performed in the mITT1 analysis set.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

Details on the definitions and analyses for the tertiary/exploratory endpoints specified in Section 3 will be described in the SAP.

9.3.5. Safety Analyses

All safety analyses will be performed on the safety population. Safety data including AEs, SAEs, AEs leading to discontinuation, vital signs, and clinical laboratory data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations in accordance with Pfizer Data Standards.

9.3.6. Other Analyses

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.

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

The following analyses will be described in a separate report and will not be included in the CSR:

- New viral lineages and/or treatment-emergent mutations with demonstrated reduced susceptibility to study intervention in vitro will be analyzed to determine the emergence of virus with reduced susceptibility in participants with mild-to-moderate COVID-19.

9.4. Interim Analyses

No formal interim analysis is planned for this study. However, the sponsor may conduct unblinded reviews of the data during the course of the study if requested by regulatory authorities including in the support of regulatory submissions. Should an unblinded review be requested, details of the unblinding plan will be described in the SAP and a separate data unblinding document.

9.5. Sample Size Determination

The study will enroll approximately 411 participants.

The sample size calculation is based on the primary efficacy endpoint as the change in viral RNA level from baseline to Day 5 as measured in NP swabs in the mITT analysis set. Assuming a SD of 1.8 (based on EPIC-HR, NCT04960202), a sample size of approximately

315 evaluable participants (210 participants in nirmatrelvir/ritonavir group and 105 participants in placebo/ritonavir group) is expected to provide 90% power to detect a difference of 0.7 $\log_{10}$ copies/mL in viral RNA between groups using a 2-sided 0.05 alpha level test. Assuming approximately 10% of participants will have a negative viral RNA result at baseline, and assuming a non-evaluable rate of 15%, approximately 411 participants will be randomized in the study to achieve approximately 315 participants evaluable for the primary efficacy endpoint.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent/Assent Process

10.1.3.1. Informed Consent Process

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

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

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

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

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

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

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

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

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

10.1.3.2. Informed Assent Process

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

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

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

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

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

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. In addition, the E-DMC may monitor the baseline SARS-CoV-2 RNA levels to ensure the population is consistent with the study design assumptions. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate safety data, to regulatory authorities and investigators, as appropriate.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results

are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and

mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

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

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

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

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

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

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

10.1.9. Study and Site Start and Closure

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

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

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

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

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

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

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

10.1.10. Publication Policy

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

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

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

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

10.1.11. Sponsor's Medically Qualified Individual

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 2. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Other	Reflex Testing
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea Serum creatinine and eGFR (calculated)[a] Glucose Sodium Potassium Chloride Total CO2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase	**Viral Serology** SARS-CoV-2 At screening: • FSH[b] • Pregnancy test (β-hCG)[c] • HIV testing[d]	For suspected DILI: AST/ALT Total bilirubin, direct and indirect bilirubin Total bile acids, GGT Total protein, albumin CK PT, INR Acetaminophen/paracetamol or protein adduct levels Hepatitis serology

a. eGFR will be calculated using the method developed by the 2021 CKD-EPI (Scr only) for participants 18 years or older or eCrCl using the Cockcroft-Gault formula for participants 12 years to <18 years.
b. FSH testing is performed locally when needed to confirm postmenopausal status at screening.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.
d. Local HIV testing at screening will be performed for participants in Germany as required by the German HA.

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

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

10.3.1. Definition of AE

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

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs using the PSSA to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and

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

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

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

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

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

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the PSSA/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical 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, which are based on the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events[30], version 2.1 (July 2017):

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each 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.

Assessment of Causality

- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the PSSA and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

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

10.3.4. Reporting of SAEs

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

SAE Reporting to Pfizer Safety via the 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

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

10.4.1. 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 10.4.3 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if at least 1 of the following conditions applies:

- Is not a WOCBP (see definition in Section 10.4.2).

  OR

- Is a WOCBP who is pregnant (at least 14 weeks gestation).

  OR

- Is a WOCBP who is not pregnant at screening and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.2. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

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

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

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

3. Postmenopausal female:

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

10.4.3. 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:

<u>Highly Effective Methods That Have Low User Dependency</u>

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.

5. Vasectomized partner:

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

Highly Effective Methods That Are User Dependent

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

    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*

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

    - Oral + barrier*
    - Injectable + barrier*

Sexual Abstinence

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

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

- Male or female condom, with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

Because ritonavir may reduce the effect of estradiol-containing contraceptives when agents are co-administered, a barrier method or other nonhormonal method of contraception should be considered if the participant is using estradiol-containing contraceptives during the 5 days of nirmatrelvir/ritonavir treatment and until 1 menstrual cycle after stopping nirmatrelvir/ritonavir.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

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

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

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

- The samples will be retained as indicated:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

eGFR (mL/min/1.73 m^2)

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	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$

Inker LA et al. N Engl J Med. 2021;385:1737-49 [32].

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

CrCl (mL/min)

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

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

10.7.2. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

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

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

Nonexhaustive lists of prohibited and precautionary medications are provided below in Table 3, and Table 4 respectively. If a medication is not listed as contraindicated, it should not automatically be assumed it is safe to coadminister. Appropriately qualified site staff will review all concomitant medications to determine if they are prohibited. The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

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

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

Table 3 lists the drugs prohibited for use with nirmatrelvir/ritonavir, and Table 4 lists clinically significant (precautionary) drugs. The drugs listed in Table 3 and Table 4 are a guide and not considered a comprehensive list of all possible drugs that may interact with nirmatrelvir/ritonavir. The healthcare provider should consult appropriate references, such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir.

Table 3. Drugs That are Contraindicated With Nirmatrelvir/Ritonavir

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

Table 3. Drugs That are Contraindicated With Nirmatrelvir/Ritonavir

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

Table 3. Drugs That are Contraindicated With Nirmatrelvir/Ritonavir

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

Table 3. Drugs That are Contraindicated With Nirmatrelvir/Ritonavir

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

Table 4. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	tamsulosin	↑ tamsulosin	Avoid concomitant use with nirmatrelvir/ritonavir.
Antiarrhythmics	lidocaine (systemic), disopyramide	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.

Table 4. Established and Other Potentially Significant Drug Interactions

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

Table 4. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole,	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate, itraconazole	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
		↑ nirmatrelvir/ritonavir	A nirmatrelvir/ritonavir dose reduction is not needed.
Anti-HIV protease inhibitors	atazanavir, darunavir,	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' prescribing information.
	tipranavir		Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased nirmatrelvir/ritonavir or protease inhibitor adverse events.
Anti-HIV	efavirenz, maraviroc, nevirapine, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↑ nevirapine ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.

Table 4. Established and Other Potentially Significant Drug Interactions

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

Table 4. Established and Other Potentially Significant Drug Interactions

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

Table 4. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			Avoid concomitant use of glecaprevir/pibrentasvir with nirmatrelvir/ritonavir.
	ombitasvir/paritaprevir/ritonavir and dasabuvir		Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information.
	sofosbuvir/velpatasvir/voxilaprevir		Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased nirmatrelvir/ritonavir or HCV drug adverse events with concomitant use.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with nirmatrelvir/ritonavir. Atorvastatin and rosuvastatin do not need to be held prior to or after completing nirmatrelvir/ritonavir.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of nirmatrelvir/ritonavir treatment and until one menstrual cycle after stopping nirmatrelvir/ritonavir.
Immunosuppressants	calcineurin inhibitors: cyclosporine, tacrolimus	↑ cyclosporine ↑ tacrolimus	Avoid concomitant use of calcineurin inhibitors with nirmatrelvir/ritonavir when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose adjustment of the immunosuppressant and close and regular monitoring for

Table 4. Established and Other Potentially Significant Drug Interactions

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

Table 4. Established and Other Potentially Significant Drug Interactions

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

Table 4. Established and Other Potentially Significant Drug Interactions

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

10.9. Appendix 9: Country-Specific Requirements

10.9.1. France

Contrat Unique

1. GCP Training

   Before enrolling any participants, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

   No participants or third-party payers will be charged for study intervention.

3. Urgent Safety Measures

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

4. Termination Rights

   Pfizer retains the right to discontinue development of nirmatrelvir/ritonavir at any time.

10.9.2. Germany

Local HIV testing at screening will be performed for participants in Germany as required by the German HA (See Appendix 2).

Protocol Inclusion Criterion 1 and associated Section 10.10.1 (Age and Sex) indicate:

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

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

Consistent with the EU conditional marketing authorization of nirmatrelvir/ritonavir, in Germany, only adult participants (≥18 years) will be enrolled in the study.

10.10. Appendix 10: Eligibility Criteria

10.10.1. Age and Sex

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

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

- Refer to Appendix 4 for reproductive criteria for female (Section 10.4.1) participants.

10.10.2. Rebound of COVID-19 Signs/Symptoms

Inclusion Criterion 2: Participants must have written documentation, such as electronic health record, medical record, or prescription receipt of treatment with nirmatrelvir/ritonavir (verbal assertion of treatment is not acceptable) with patient-reported 100% compliance (ie, completed a 5 day course of nirmatrelvir/ritonavir). They must have symptom alleviation or resolution in COVID-19 signs/symptoms followed by a worsening (rebound) of signs/symptoms after completing an initial 5-day course of nirmatrelvir/ritonavir based on the judgement of both the participant and investigator.

10.10.3. SARS-CoV-2 Infection

Inclusion Criterion 5: SARS-CoV-2 infection as determined by rapid antigen testing in any specimen collected within 24 hours prior to randomization and collected within 2 weeks (14 days) after the completion of the initial 5-day treatment course of nirmatrelvir/ritonavir.

Note: If rapid antigen testing is performed at screening and baseline, the baseline result will determine eligibility.

10.10.4. Risk of Developing Severe Illness from COVID-19

Inclusion Criterion 6: Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:

- Age ≥60 years;

- BMI ≥25 kg/m^2 (or ≥85th percentile for pediatric participants);

- Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes;

- Chronic lung disease (if asthma requires daily prescribed therapy);

- Diagnosis of hypertension;

- CVD, defined as history of any of the following: myocardial infarction, TIA, stroke, HF, angina with prescribed nitrate, CABG, PCI, carotid endarterectomy, aortic bypass, peripheral arterial disease;
- Congenital heart disease;
- Type 1 or Type 2 diabetes mellitus;
- CKD provided the participant does not meet exclusion criterion #5;
- Chronic liver disease (provided the participant does not meet exclusion criterion #2);
- Sickle cell disease or thalassemia;
- Dementia, neurodevelopmental disorders (eg, cerebral palsy, Down syndrome) or other conditions that confer medical complexity (eg, genetic or metabolic syndromes and severe congenital anomalies);
- Active cancer, other than localized skin cancer, provided that the subject does not meet the exclusion criterion for being immunocompromised (Section 5.2, Exclusion Criterion 7);
- Medical-related technological dependence (eg, CPAP [not related to COVID-19]).

Exclusion Criterion 6: Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization.

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

10.10.5. Prior/Concomitant Therapy

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

- Current any medications that are highly dependent on CYP3A4 for clearance and which are contraindicated in combination with nirmatrelvir/ritonavir (see Appendix 8). Coadministration of nirmatrelvir/ritonavir with other medications that are not contraindicated but are highly dependent on CYP3A4 for clearance may require dose adjustment or additional monitoring (See Appendix 8 in protocol).
- Use of any medications or substances that are strong inducers of CYP3A4 and that are contraindicated in combination with nirmatrelvir/ritonavir without the appropriate washout prior to the first dose of nirmatrelvir/ritonavir (see Appendix 8 in protocol). The appropriate washout period for CYP3A4 inducers should be determined based on the prescribing information for the concomitant medication and in consultation with the medical monitor.

10.10.6. Other Treatments for COVID-19

Exclusion Criterion 11: Receiving other COVID-19 specific treatments within 30 days of randomization and through Day 34, including but not limited to COVID-19 antivirals (excluding a single 5-day treatment course of nirmatrelvir/ritonavir that qualifies a participant for eligibility), monoclonal antibodies for COVID-19.

10.10.7. Immunocompromised Criteria Details

Exclusion Criterion 7: Immunocompromised with ≥1 of the following:

1. Solid organ (eg, liver, heart, lung or kidney) transplant recipient who is receiving immunosuppressive therapy;

2. Receipt of CAR-T cell therapy or HCT either within 2 years of transplantation or who are receiving immunosuppressive therapy;

3. Moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott Aldrich syndrome);

4. Use of at least 1 of the following immune-weakening medications:

    a. Has received corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry.

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

5. Active immunosuppressive treatment for solid tumor;

6. Hematological malignancy (including leukemia, lymphoma, and myeloma);

7. Advanced or untreated HIV infection defined as CD4 cell counts <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV.

10.11. Appendix 11: Participant-Reported COVID-19-Related Signs and Symptoms

Sign and Symptom Collection[33]	Eligibility Criterion #5 Targeted (used for study entry)	Signs and Symptom Collection
Cough	X	X
Shortness of breath or difficulty breathing	X	X
Fever (documented temperature >38˚C [100.4˚F]) or subjective fever (eg, feeling feverish)	X	
Feeling feverish		X
Chills or shivering	X	X
Fatigue (low energy or tiredness)	X	X
Muscle or body aches	X	X
Diarrhea (loose or watery stools)	X	X
Nausea (feeling like you wanted to throw up)	X	X
Vomiting (throw up)	X	X
Headache	X	X
Sore throat	X	X
Stuffy or runny nose	X	X
Loss of smell	X	X
Loss of taste	X	X

10.12. Appendix 12: Protocol Amendment History

Amendment 1 (16 September 2022)

Overall Rationale for the Amendment: Modifications to the estimands, primary analysis population, as well as a change in one of the secondary endpoints which resulted in additional procedures necessitated this amendment. Also included in this amendment are updated DDI tables, removal of RT-PCR testing as an option to determine eligibility, addition of a tertiary endpoint, corrections, and general editorial changes to correct grammatical errors, to maintain consistency, and/or to increase clarity

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial.
1.1 Synopsis, 3. OBJECTIVES, ENDPOINTS AND ESTIMANDS, 9.1.1.1 Primary Estimand, 9.1.1.2 Secondary Estimand, 9.2 Analysis Set and 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis 2	The population in the estimands and the primary analysis population was updated with the requirement of a positive rapid antigen test at baseline to align with the inclusion/exclusion criteria.	More inclusive and generalizable.	Substantial
1.1 Synopsis, 3. OBJECTIVES, ENDPOINTS AND ESTIMANDS, 9.1.1.2 Secondary Estimands and 9.1.2 Multiplicity Adjustment	Endpoint of: 'Proportion of participants with SARS-CoV-2 RNA in NP swabs below the LLOQ (defined as <2.0 $\log_{10}$ copies/mL) on both Days 5 and 10'. Removed as a secondary endpoint and added as a tertiary/exploratory endpoint.	Replaced with a new secondary endpoint	Substantial
1.1 Synopsis, 3. OBJECTIVES, ENDPOINTS AND ESTIMANDS, 9.1.1.2 Secondary Estimands, 9.1.2 Multiplicity Adjustment and 9.3.3 Secondary Endpoints	New secondary endpoint/estimand of: 'Time to 2 consecutive negative rapid antigen test results.' Added. The corresponding analysis for secondary endpoints were updated /added with more details.	Based on regulatory feedback	Substantial
1.1 Synopsis and 9.5 Sample Size Determination	Updated sample size assumptions and the corresponding calculation to reflect the change in the primary analysis population.	To align with the changes in primary analysis population and eligibility criteria.	Substantial
1.3. Schedule of Activities, 8.7.3. Rapid Antigen Assessments, and 10.10.3 SAR-CoV-2 Infection	Amended to add self-administered daily rapid antigen tests for all study days between scheduled visits until 2 consecutive negative rapid antigen test results are obtained at which point, rapid antigen testing will be performed only at remaining scheduled visits.	Necessary to support new secondary endpoint	Substantial
10.8 Appendix 8: Prohibited Concomitant Medications That May Result in DDI	Text describing Tables 4 and 5 was revised to clarify DDI table content. Tables were updated with information from the Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid (August 2022).	Updates to the list of precautionary and prohibited medications.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial.
3. OBJECTIVES, ENDPOINTS AND ESTIMANDS	New tertiary endpoint of: 'Time (days) to sustained resolution of all targeted signs and symptoms through Day 28 where sustained resolution is defined as the first of two consecutive days when all targeted COVID-19 symptoms are scored as absent. ' added	Based on regulatory feedback,	Nonsubstantial
1.3 Schedule of Activities, Section 8.7.1 Viral RNA Assessment (NP Swab) and 8.7.3 Rapid Antigen Assessments	Clarified in Section 8.7.1 that NP swab collection must occur prior to rapid antigen assessment, and clarified in SoA notes and Section 8.7.3 that rapid antigen testing must occur after NP swab collection.	To ensure that assessments for the primary endpoint are prioritized.	Nonsubstantial
4.2 Scientific Rational for Study Design and 6.9 Prior and Concomitant Therapy	Described ritonavir as an inhibitor of CYP3A4 and provided guidance accordingly.	To provide clinical guidance for participants who take concomitant medications metabolized by CYP3A4.	Nonsubstantial
5.1 Inclusion Criteria and 10.10.3 and throughout the protocol	Removal of 'confirmed' in relation to SARS-CoV-2 infection	'Confirmed' is generally used in association with RT-PCR testing which has been removed from the protocol	Nonsubstantial
6.1.1 Administration	Updated timing of dose administration.	To align with dosing administration in other C467 protocols.	Nonsubstantial
8.1. Administrative and Baseline Procedures	The total blood sampling volume reduced to approximately 160 mL.	More refined estimate of total blood volume received from central laboratory for the study.	Nonsubstantial
8.1.1.2 Secondary Contacts	Added that secondary contacts may be used to determine if a participant is lost to follow-up or vital status check.	To clarify utility of collecting secondary contact information.	Nonsubstantial
8.7.6.1. Plasma for Protein Analysis	Blood sample volume reduced to 6 mL.	More refined estimate of blood volume received from central laboratory for the study.	Nonsubstantial
10.1.5 Data Monitoring Committee	Including E-DMC monitoring of baseline SARS-CoV-2 RNA levels.	To ensure population is consistent with study design assumptions.	Nonsubstantial
10.2 Appendix 2: Clinical Laboratory Tests	Clarified that FSH testing if needed is to be performed locally.	Correction	Nonsubstantial
10.10.4. Risk of Developing Severe Illness from COVID-19	Added Age ≥60 years.	Correction	Nonsubstantial
10.4.1 Female Participant Reproductive Inclusion Criteria	Text updated for consistency with other C467 studies.	Updated to align with other C467 protocols	Nonsubstantial
Throughout the protocol	Remove RT-PCR	To simplify eligibility assessment, SARS-CoV-2 infection will be confirmed by rapid antigen test only	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial.
Throughout the protocol	General editorial changes.	To correct grammatical errors, to maintain consistency, and/or to increase clarity.	Nonsubstantial

Amendment 2 (01 February 2023)

Overall Rationale for the Amendment: The German HA has requested for all participants to be enrolled in Germany to undergo HIV testing at screening. Participants who do not consent to the screening HIV test will not be able to participate in the study. In addition, consistent with the EU conditional marketing authorization of nirmatrelvir/ritonavir, this amendment clarifies that in Germany, only adult participants (≥18 years) will be enrolled in the study.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial.
SoA, Table 2, Section 10.9.2 Country Specific Requirements	HIV diagnostics at screening added to the laboratory assessments for participants in Germany.	As above.	Nonsubstantial
Title page	Added Clinicaltrials.gov ID	The ID became available at the time of the protocol amendment.	Nonsubstantial
Multiple sections throughout	Minor text updates to clarify protocol text and correct minor errors and typos from previous versions.	To clarify protocol text and correct inadvertent errors.	Nonsubstantial

Amendment 3 (12 May 2023)

Overall Rationale for the Amendment: The protocol was primarily amended to update the primary analysis population. Additional revisions are noted in the table below.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Primary and secondary estimands and the mITT analysis set description have been updated to include that participants must have a positive viral RNA NP swab test result at baseline.	The study primary endpoint is based on change in viral SARS-CoV-2 RNA level measured in NP swabs from Baseline to Day 5, therefore a quantifiable viral RNA NP swab test result at baseline is necessary to enable assessment of the primary endpoint.	Section 1.1 Synopsis Section 3 Objectives, Endpoints, and Estimands Section 9.1.1.1 Primary Estimand Section 9.1.1.2 Secondary Estimands Section 9.2 Analysis Sets
Sample size calculation updated.	To align with the update for primary analysis population.	Section 9.5 Sample Size Determination
Non-substantial Modification(s)		
Update to text regarding viral RNA assessments (NP swab) and rapid antigen assessments.	To align with changes introduced with Protocol Amendment 01 (16 Sep 2022) because as noted in the Summary of Changes table within Protocol Amendment 01, SARS-CoV-2 infection is required to be confirmed by rapid antigen test only (PACL dated 03 Oct 2022). To clarify that the Screening and Baseline (Day 1) visits are exempt from the protocol-directed sequencing of NP and RAT (PACL dated 01 Nov 2022).	Section 1.3 Schedule of Activities Section 8.7.1 Viral RNA Assessment (NP Swab) Section 8.7.3 Rapid Antigen Assessments
Update to inform that the EMA has granted marketing authorization approval for nirmatrelvir/ritonavir.	To update the regulatory status of nirmatrelvir/ritonavir in the EU.	Section 2.3.2 Benefit Assessment
Minor editorial updates including link to Table 3 in Appendix 8.	For clarification and to guide the reviewer to the correct Table in Appendix 8.	Section 6.9 Prior and Concomitant Therapy
Minor editorial updates.	To correct grammatical errors, to maintain consistency, and/or to increase clarity, and align with the most current protocol template (14 Apr 2023).	Throughout the protocol, including: Section 10.1.3.2 Informed Assent Process Section 10.1.4 Data Protection Section 10.1.6 Dissemination of Clinical Study Data Section 10.1.7 Data Quality Assurance Section 10.1.9 Study and Site Start and Closure

Description of Change	Brief Rationale	Section # and Name
		Section 10.1.10 Publication Policy
Updated text on the contraception requirements during the 5 days of nirmatrelvir/ritonavir treatment.	Updated to align with the latest version of the USPI (dated 18 Apr 2023)	Section 10.4.3 Contraception Methods
Updated section header. Updates to Table 3 (Drugs That are Contraindicated With Nirmatrelvir/Ritonavir) and Table 4 (Established and Other Potentially Significant Drug Interactions)	Updated to align with the latest version of the USPI (dated 18 Apr 2023)	Section 10.8 Appendix 8

10.13. Appendix 13: Abbreviations

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

Abbreviation	Term
Abs	absolute
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
b-hCG	b-human chorionic gonadotropin
BP	blood pressure
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
CT	computed tomography/clinical trial
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	end of treatment
EPIC-HR	Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients
eSAE	electronic serious adverse event

Abbreviation	Term
ESR	erythrocyte sedimentation rate
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HA	health authority
HCP	health care professional
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRT	Interactive Response Technology
JAK	Janus Kinase
KDIGO	Kidney Disease: Improving Global Outcomes
LFT	liver function test
LLOQ	lower limit of quantitation
LTFU	long-term follow up
mITT	modified intent-to-treat
MMRM	mixed model repeated measures approach
MQI	medically qualified individual
NA	not applicable
NCT	National Clinical Trial
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
NP	nasopharyngeal
OP	oropharyngeal
PACL	protocol administrative change letter
PDE5	phosphodiesterase-5
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant

Abbreviation	Term
PT	prothrombin time
QTL	quality tolerance limit
RAT	rapid antigen test
RBC	red blood cell
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
Scr	serum creatinine
Scys	serum cystatin C
sGC	soluble guanylate cyclase
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	telemedicine
T bili	total bilirubin
TCID50	Median Tissue Culture Infectious Dose
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

1. Carlin AF, Clark AE, Chaillon A, et al. Virologic and Immunologic Characterization of COVID-19 Recrudescence after Nirmatrelvir/Ritonavir Treatment. Preprint: 18 May 2022. Clin Infect Dis. 2022;10.1093/cid/ciac496.
2. Gupta K. SJ, Stack G., et al. Rapid Relapse of Symptomatic SARS-CoV-2 Infection Following Early Suppression with Nirmatrelvir/Ritonavir. Preprint 26 Apr 2022. Report Number: v1. 2022. Available from: https://doi.org/10.21203/rs.3.rs-1588371/v1.
3. Charness M. GK, Stack G., Strymish J., Adams E., Lindy D., Mohri H., and Ho D. Rapid Relapse of Symptomatic Omicron SARS-CoV-2 Infection Following Early Suppression with Nirmatrelvir/Ritonavir. 2022. Available from: https://www.researchsquare.com/article/rs-1588371/v3.
4. Julie Boucau RU, Caitlin Marino, James Regan, James P. Flynn, Manish C. Choudhary, Geoffrey Chen, Ashley M. Stuckwisch, Josh Mathews, May Y. Liew, Arshdeep Singh, Zahra Reynolds, Surabhi L. Iyer, Grace C. Chamberlin, Tammy D. Vyas, Jatin M. Vyas, Sarah E. Turbett, Jonathan Z. Li, Jacob E. Lemieux, Amy K. Barczak, Mark J. Siedner. Virologic characterization of symptom rebound following nirmatrelvir-ritonavir treatment for COVID-19. medRxiv. 2022.
5. Ranganath N, O'Horo JC, Challener DW, et al. Rebound Phenomenon after Nirmatrelvir/Ritonavir Treatment of Coronavirus Disease-2019 in High-Risk Persons. Clin Infect Dis. 2022;10.1093/cid/ciac481.
6. US Food and Drug Administration. Guidance for assessing COVID-19-related symptoms in outpatient adult and adolescent subjects in clinical trials of drugs and biological products for COVID. 2020. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-covid-19-related-symptoms-outpatient-adult-and-adolescent-subjects-clinical-trials-drugs. Accessed: 29 June 2021.
7. John Hopkins University. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Available from: https://coronavirus.jhu.edu/map.html. Accessed on: Jun 2020.
8. US Food and Drug Administration. COVID-19 Vaccines. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines. Accessed on: 29 Jun 2021.
9. US Food and Drug Administration. Fact sheet for healthcare providers emergency use authorization of Paxlovid™. Available from: https://www.fda.gov/media/155050/download. Accessed: 27 July 2022.
10. US Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Molnupiravir. February 2022. Available from: https://www.fda.gov/media/155054/download. Accessed: 22 February 2022.
11. Veklury® (Remdesivir) Significantly Reduced Risk of Hospitalization in High-Risk Patients with COVID-19 Available at: https://www.gilead.com/news-and-press/press-room/press-releases/2021/9/veklury-remdesivir-significantly-reduced-risk-of-hospitalization-in-highrisk-patients-with-covid19 [press release]. 22 Sep 2021.
12. Pfizer. Investigator's Brochure PF-07321332. Data on file.

13. European Medicines Agency. Paxlovid (PF-07321332/ritonavir). Available from: https://www.ema.europa.eu/en/documents/overview/paxlovid-epar-medicine-overview_en.pdf. Accessed: 27 Apr 2023.
14. Nakajima Y, Ogai A, Furukawa K, et al. Prolonged viral shedding of SARS-CoV-2 in an immunocompromised patient. J Infect Chemother. 2021;27(2):387-89.
15. Baang JH, Smith C, Mirabelli C, et al. Prolonged Severe Acute Respiratory Syndrome Coronavirus 2 Replication in an Immunocompromised Patient. J Infect Dis. 2021;223(1):23-27.
16. Administration UFD. (2022). Fact Sheet For Patients, Parents, and Caregivers. Emergency Use Authorization (EUA) of PAXLOVID For Coronavirus Disease 2019 (COVID-19). Available from: https://www.fda.gov/media/155051/download. Accessed on: March 3.
17. Food and Drug Administration Guidance for Industry: FDA Guidance for Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment. [Internet]. 2020. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-covid-19-related-symptoms-outpatient-adult-and-adolescent-subjects-clinical-trials-drugs.
18. Ware J KM, Bjorner J, et al. Development User's Manual for the SF-36v2® Health Survey. QualityMetric Incorporated; 2007.
19. US Bureau of Labor Statistics. Effects of COVID-19 Pandemic on Productivity and Costs Statistics. Available from: https://www.bls.gov/covid19/effects-of-covid-19-pandemic-on-productivity-and-costs-statistics.htm. Accessed on: 08 Jun 2021.
20. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353-65.
21. Rabin R, Gudex C, Selai C, et al. From translation to version management: a history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. Value Health. 2014;17(1):70-6.
22. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.
23. Ramos-Goni JM, Pinto-Prades JL, Oppe M, et al. Valuation and Modeling of EQ-5D-5L Health States Using a Hybrid Approach. Med Care. 2017;55(7):e51-e58.
24. Yang Y, Brazier J, Longworth L. EQ-5D in skin conditions: an assessment of validity and responsiveness. Eur J Health Econ. 2015;16(9):927-39.
25. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-27.
26. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
27. Agborsangaya CB, Lahtinen M, Cooke T, et al. Comparing the EQ-5D 3L and 5L: measurement properties and association with chronic conditions and multimorbidity in the general population. Health Qual Life Outcomes. 2014;12:74.
28. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.

29. U.S. Department of Health and Human Services NIoH, National Heart, Lung, and Blood Institute. A Pocket Guide to Blood Pressure Measurement in Children. May 2007. Available from: https://www.nhlbi.nih.gov/files/docs/bp_child_pocket.pdf. Accessed: 16 February 2022.
30. U.S. Department of Health and Human Services NIoH, National Institute of Allergy and Infectious Diseases, Division of AIDS,. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. July 2017. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Accessed: 10 Jun 2021.
31. Benjamini Y, & Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. . Journal of the Royal Statistical Society. 1995;57:289–300.
32. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737-49.
33. US Food and Drug Administration. Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment. 2020. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-covid-19-related-symptoms-outpatient-adult-and-adolescent-subjects-clinical-trials-drugs. Accessed: 25 Mar 2021.

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