Title Page

A PHASE 1, OPEN-LABEL, NON-RANDOMIZED STUDY TO INVESTIGATE THE SAFETY AND PK FOLLOWING MULTIPLE ORAL DOSES OF PF-07321332 (NIRMATRELVIR)/RITONAVIR IN ADULT PARTICIPANTS WITH COVID-19 AND SEVERE RENAL IMPAIRMENT EITHER ON HEMODIALYSIS OR NOT ON HEMODIALYSIS

Study Intervention Number:	PF-07321332/Ritonavir
Study Intervention Name:	PF-07321332 (nirmatrelvir)/ritonavir
US IND Number:	153517
EudraCT Number:	2023-503870-19-00
ClinicalTrials.gov ID:	NCT05487040
Pediatric Investigational Plan Number	NA
Protocol Number:	C4671028
Phase:	1

Brief Title: A Phase 1, Open-label, Non-randomized Safety and PK Study of Multiple Oral Doses of PF-07321332 (Nirmatrelvir)/Ritonavir in Adult Participants with COVID-19 and Severe Renal Impairment

Document History

Document	Version Date
Amendment 2	09 Feb 2023
Amendment 1	23 Jun 2022
Original protocol	25 Mar 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 2 (09 Feb 2023)

Overall Rationale for the Amendment: To add additional blood to plasma ratio sample either on Day 3 or Day 4 or Day 5 in Cohort 1 and on Day 1 in Cohort 2; and to provide additional clarification on blood to plasma ratio sample processing.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Title page	Added EudraCT number and ClinicalTrials.gov ID	EudraCT number and ClinicalTrials.gov ID are now available for this study.	Nonsubstantial
Section 1.3. Schedule of Activities – PK Sampling Schemas 1-12; Section 8.5.3 PK Samples for Analysis of PF-07321332 (nirmatrelvir) and Ritonavir; Section 8.5.4. Blood to Plasma Ratio Analysis of PF-07321332 (nirmatrelvir) and ritonavir	Updates to implement collection of 1 additional blood to plasma ratio sample at steady state. Flexibility to collect the sample on a different day if a sample was missed.	This additional blood to plasma ratio sample will help in providing accurate normalization for Tasso PK when compared with nirmatrelvir/ritonavir plasma concentrations.	Substantial
Section 9.4 Interim Analyssis	Added text for unblinded reviews of the data	Added text based on text in SAP.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Title page	Added EudraCT number and ClinicalTrials.gov ID	EudraCT number and ClinicalTrials.gov ID are now available for this study.	Nonsubstantial
Section 1.3 SoA; Section 10.2. Clinical Laboratory Tests, Table 3; Section 10.9.1. Country Specific Requirements	HIV test at screening added to the laboratory assessments for participants in Germany.	The German Health Authority 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.	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1, Open-Label, Non-Randomized Study to Investigate the Safety and PK Following Multiple Oral Doses of PF-07321332 (Nirmatrelvir)/Ritonavir in Adult Participants with COVID-19 and Severe Renal Impairment Either on Hemodialysis or not on Hemodialysis.

Brief Title: A Phase 1, Open-label, Non-randomized Safety and PK Study of Multiple Oral Doses of PF-07321332 (Nirmatrelvir)/Ritonavir in Adult Participants with COVID-19 and Severe Renal Impairment.

Regulatory Agency Identification Number(s):

US IND Number:	153517
EudraCT Number:	NA
ClinicalTrials.gov ID:	NCT05487040
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4671028
Phase:	1

Rationale:

The purpose of this study is to evaluate the safety and PK of PF-07321332 (nirmatrelvir)/ritonavir in adults with severe renal impairment and COVID-19. Eligible participants include those with severe renal impairment (defined as eGFR <30 mL/min/1.73 m^2) and not yet receiving HD (Cohort 1) and individuals receiving HD (Cohort 2).

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To describe the safety and tolerability of PF-07321332 (nirmatrelvir)/ritonavir in adult participants with COVID-19 and severe renal impairment.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	• Not Applicable.

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the effect of severe renal impairment on the PK of PF-07321332 (nirmatrelvir) in participants not on HD. • To evaluate the effect of severe renal impairment on the PK of PF-07321332 (nirmatrelvir) in participants on HD.	• Plasma PF-07321332 (nirmatrelvir) PK parameters including C_{max}, CL/F, Vz/F, $AUC_{0\text{-}tau}$, $t_{½}$, and C_{trough} estimated from the population PK model.	• Not Applicable.
• To evaluate the effect of HD on the PK of PF-07321332 (nirmatrelvir).	• HD clearance (CLd) of PF-07321332 (nirmatrelvir). • Fraction of PF-07321332 (nirmatrelvir) dose removed from the body by dialysis (Fd).	• Not Applicable.

Overall Design:

This is a Phase 1, open-label study to evaluate the effect of severe renal impairment on the PK of PF-07321332 (nirmatrelvir)/ritonavir and the safety and tolerability of PF-07321332 (nirmatrelvir)/ritonavir in non-hospitalized adult participants with COVID-19 and severe renal impairment and not yet receiving intermittent HD (Cohort 1) and severe renal impairment receiving intermittent HD (Cohort 2). The study will be conducted in 2 parallel cohorts. Cohort 1 will enroll eligible participants with severe renal impairment (defined as eGFR <30 mL/min/1.73 m^2) and not on HD. Cohort 2 will enroll eligible participants with severe renal impairment and on HD. All eligible participants will be assigned to receive a single dose of PF-07321332 (nirmatrelvir)/ritonavir 300 mg/100 mg orally on Day 1 followed by PF-07321332 (nirmatrelvir)/ritonavir 150 mg/100 mg QD from Day 2 to Day 5. Population PK model-based simulations showed that the PF-07321332 (nirmatrelvir) single dose of 300 mg on Day 1 followed by 150 mg of PF-07321332 (nirmatrelvir) QD on Day 2 to Day 5 with ritonavir 100 mg in severe renal impaired participants gives comparable exposure ($AUC_{0\text{-}24}$ and C_{max}) to COVID-19 patients with normal renal function at the 300 mg PF-07321332 (nirmatrelvir)/ 100 mg ritonavir BID dose for 5 days. Published reports and internal data (C4671011 data on file) show ritonavir PK is comparable between normal healthy participants and severe renal impairment patients and only small fraction of ritonavir dose is removed by HD.[1, 23, 24] Ritonavir 100 mg QD or BID dose has been used for several protease inhibitors (eg, darunavir) with small difference in dose normalized C_{trough} of protease inhibitors. Additionally, the PK of PF-07321332 (nirmatrelvir) with 100 mg QD of ritonavir in severe renal impairment participants is expected to be similar to those of healthy

participants taking 100 mg BID of ritonavir. Therefore, the ritonavir dose of 100 mg QD was selected for this study.

This study will use the program-level E-DMC which is independent of the study team and includes only external members, and is responsible for the ongoing monitoring of the efficacy and safety of participants in the program's studies according to the E-DMC charter (Section 10.1.5.1).

Number of Participants:

Approximately 24 participants (12 participants in Cohort 1 and 12 participants in Cohort 2) will be assigned to study intervention.

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 assignment to study intervention. 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:

Age and Sex:

1. Participants ≥18 years of age (or the minimum country specific age of consent if >18) at the time of the Screening Visit.

    - WOCBP may be enrolled.

    - WOCBP must agree to use an effective method of contraception described in Section 5.3. Refer to Appendix 4 for reproductive criteria for male and female participants.

Disease Characteristics:

2. Mild-to-moderate COVID-19 disease as defined in Appendix 9 with confirmed SARS-CoV-2 infection in any specimen collected within 5 days prior to treatment assignment.

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

3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of treatment assignment.

Other Inclusion Criteria:

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

Additional Inclusion Criteria for Cohort 1 (Severe Renally Impaired and not on HD):

5. Severe renal impairment defined as eGFR <30 mL/min/1.73m^2 (using the 2021 CKD-EPI serum creatinine only eGFR formula in Section 10.7.2.1) measured by clinical laboratory testing on at least 2 occasions, one of which must be within 3 months of Screening and not receiving intermittent HD treatments.

Additional Inclusion Criteria for Cohort 2 (Receiving HD):

6. Receiving stable intermittent HD for at least 6 weeks prior to Screening.

Exclusion Criteria

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

Medical Conditions:

1. Current need for hospitalization or anticipated need for hospitalization within 48 hours after treatment assignment in the clinical opinion of the site investigator.

2. Renal transplant recipients.

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

4. Known HIV infection with viral load >400 copies/mL or HIV infection with CD4+ cell count <200/mm^3.

    - Participants in Germany will be excluded if the screening HIV test is positive or if they do not consent to have an HIV test at screening.

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

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

7. 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:

8. Current use of any medications that are highly dependent of CYP3A4 for clearance and which are contraindicated in combination with PF-07321332 (nirmatrelvir)/ritonavir (Appendix 8). Participants taking lovastatin and simvastatin may enroll, provided that they have discontinued use at least 12 hours prior to initiation of PF-07321332 (nirmatrelvir)/ritonavir and refrain from use during treatment and for 5 days after the last dose of PF-07321332 (nirmatrelvir)/ritonavir. Coadministration of PF-07321332 (nirmatrelvir)/ritonavir with medications that are highly dependent on CYP3A4 for clearance may require dose adjustment or additional monitoring (See Appendix 8).

9. Use of any medications or substances that are strong inducers of CYP3A4 and that are contraindicated in combination with PF-07321332 (nirmatrelvir)/ritonavir without the appropriate washout prior to the first dose of PF-07321332 (nirmatrelvir)/ritonavir (see 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.

10. Has received or is expected to receive mAb treatment, convalescent COVID-19 plasma, or anti-viral treatment (eg, molnupiravir, remdesivir) for the current SARS-CoV-2 infection (See Section 6.9).

Prior/Concurrent Clinical Study Experience:

11. Is unwilling to abstain from participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 therapeutics, through the end of study. Previous administration with any investigational 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).

12. Known prior participation in this trial or other trial involving PF-07321332 (nirmatrelvir).

Diagnostic Assessments:

None.

Other Exclusion Criteria:

13. Females who are pregnant or breastfeeding.

14. 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 will receive a single dose of PF-07321332 (nirmatrelvir)/ritonavir 300 mg/100 mg orally on Day 1 followed by PF-07321332 (nirmatrelvir)/ritonavir 150 mg/100 mg QD from Day 2 to Day 5. The total study duration is up to 38 days and includes a 1-to-2-day screening period where participants can be screened on one day and randomized the next day or screened and randomized on the same day. Screening procedures can be performed over 2 days, but the participant must be randomized by the second day (Day 1) and begin study treatment. Therefore, Screening and Randomization can take no longer than 2 consecutive days. After Screening, the participant takes study intervention for 5 days and completes the safety follow-up period through Day 34. This equates to a total study duration of up to 38 days.

Study Intervention(s)	
Intervention Name	PF-07321332 (nirmatrelvir)/ritonavir
Arm Name (group of participants receiving a specific treatment or no treatment)	All participants will receive the same treatment open-label
Unit Dose Strength(s)	PF-07321332 (nirmatrelvir) 150 mg Ritonavir 100 mg
Route of Administration	Oral
Use	Experimental
IMP or NIMP/AxMP	IMP

Study Arm(s)	
Arm Title	PF-07321332 (nirmatrelvir)/ritonavir (5-Days)
Arm Type	Experimental
Arm Description	Participants will receive PF-07321332/ritonavir 300 mg/100 mg on Day 1 followed by PF-07321332/ritonavir 150 mg/100 mg QD from Day 2 to Day 5.

Statistical Methods:

The sample size of 12 evaluable participants per cohort is considered to provide a suitable estimate of the precision of PK parameters of PF-07321332 (nirmatrelvir) in severe renal impairment patients on HD and not on HD, as this provided 40% precision (the width of 90% CI) for AUC_{inf} and C_{max}. To ensure sufficient PK data for analysis, any participant with insufficient PK samples for analysis may be replaced.

TEAEs will be summarized with the number and percent of participants in the SAS through Day 34 for two cohorts and overall.

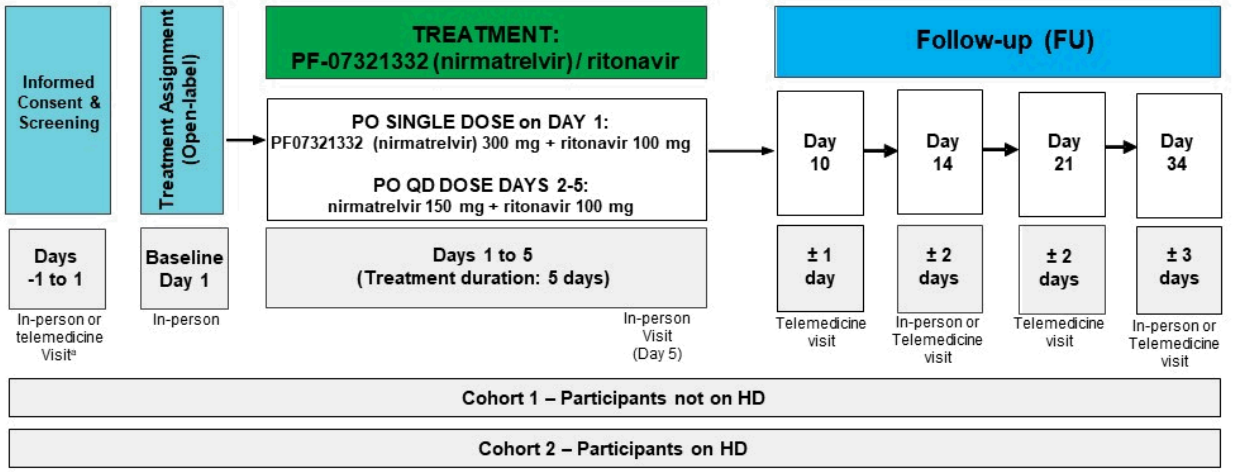
For summary statistics by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used. PF-07321332 (nirmatrelvir)/ritonavir plasma concentration data will be analyzed using a population PK analysis approach (nonlinear mixed effects models). Box and whisker plots for individual participant parameters (AUC_{inf} and C_{max}) will be constructed by each cohort and overlaid with geometric means.

Ethical Considerations:

Data from the Phase 3 study (Study C4671005) support the use of PF-07321332 (nirmatrelvir)/ritonavir in patients who are at high-risk for progression to severe COVID-19 including hospitalization or death. Patients with severe renal impairment affected by COVID-19 are considered at high-risk of progressing to severe infection. PF-07321332 (nirmatrelvir) PK and safety was evaluated in severe renal impairment (Study C4671011). A single dose of PF-07321332 (nirmatrelvir) 100 mg/ritonavir 100 mg was generally safe and well-tolerated in both healthy and renally impaired adult participants (Study C4671011).

Given the limited treatment options to treat COVID-19 infections in the severe renal impairment population, participants may experience the benefit of improvement of the clinical course of their SARS-CoV-2 infection through participation in this study while receiving close monitoring and more frequent assessments compared to the standard of care. PK and safety in PF-07321332 (nirmatrelvir) has not yet been evaluated in HD patients. The study design will be open-label and will allow for close monitoring for any potential safety events related to PF-07321332 (nirmatrelvir)/ritonavir in the severe renal impairment population both on and not on HD.

1.2. Schema



a. Screening and baseline visits may be a combination of in-person and telemedicine visits. Screening period is 1-2 days and participants can be screened and randomized on the same day but must be randomized by the second day (Day 1 of study intervention).
b. The Baseline/Day 1 visit must be in person at the site.
c. In-person visits at Days 14 and 34 are required only if procedures per SoA need to be performed or if clinically relevant abnormal laboratory values were present from a sample drawn at the previous study visit and need to be repeated.

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.

Visit Identifier	Screening	Baseline (Day 1)	Day 5	Day 10	Day 14	Day 21	Day 34	ET	Notes
Visit Window	**Day -1 to Day 1**	**0 days**	**0 days**	**±1 day**	**±2 days**	**±2 days**	**±3 days**		
Type of Visit	**In-Person Site or Home Health Visit with Telehealth**	**In-Person Site Visit**	**In-Person Site or Home Health Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	
ELIGIBILITY									
Informed consent	X								• See Section 10.1.3.
Verify inclusion/exclusion criteria	X								• See Sections 5.1 and 5.2.
Demographics and medical history	X								• COVID-19 vaccination status will be collected as part of the medical history.
PHYSICAL EXAMINATION & VITAL SIGNS									
Targeted physical examination	X	X	X		[X]		[X]	[X]	• Will be completed at all in-person visits. If not done at Screening, the procedures listed may be completed on Day 1 to assess eligibility prior to randomization and dispensing treatment. • Previously identified AEs (either by interview, physical exam, or other assessment) should be monitored to the extent possible if telehealth is used. • Targeted physical examinations see Section 8.3.1.
Vital signs	X	X	X						• Vital signs see Section 8.3.3. (Further details for HD treatment days).

Visit Identifier	Screening	Baseline (Day 1)	Day 5	Day 10	Day 14	Day 21	Day 34	ET	Notes
Visit Window	**Day -1 to Day 1**	**0 days**	**0 days**	**±1 day**	**±2 days**	**±2 days**	**±3 days**		
Type of Visit	**In-Person Site or Home Health Visit with Telehealth**	**In-Person Site Visit**	**In-Person Site or Home Health Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	
Weight, height	X	X							• Height may be self-reported. • HD treatment days will require database entry of pre- and post-dialysis weight. See Section 8.3.2.
LABORATORY									
Hematology	[X]	X	X		[X]		[X]	[X]	• Screening visit: Laboratory assessments are not required at screening unless deemed necessary by the investigator to confirm eligibility. The medical laboratory test abnormalities within 3 months prior to screening must be closely assessed. • Screening visit: If Laboratory assessments cannot be verified within 3 months of screening, local laboratory testing should be performed at screening to confirm eligibility for the study. • Baseline laboratory assessments should be collected prior to first dose of study intervention. • SARS-CoV-2 serology sample should be collected if an in-person (in clinic or home health) visit is conducted at Day 14 ±2, Day 34 ±3 or ET visits. • Safety laboratory tests (hematology, blood chemistry) at Days 14±2 and 34±3 /ET are required only if clinically significant abnormal laboratory values were present from a sample drawn at the previous study visit when laboratory assessments were performed. • Abnormal laboratory values related to AEs should be followed until resolution. See Section 8.3.4 and Appendix 2.
Blood chemistry	[X]	X	X		[X]		[X]	[X]	
SARS-CoV-2 Serology (IgG and IgM)	[X]	X	X		[X]		[X]	[X]	

Visit Identifier	Screening	Baseline (Day 1)	Day 5	Day 10	Day 14	Day 21	Day 34	ET	Notes
Visit Window	**Day -1 to Day 1**	**0 days**	**0 days**	**±1 day**	**±2 days**	**±2 days**	**±3 days**		
Type of Visit	**In-Person Site or Home Health Visit with Telehealth**	**In-Person Site Visit**	**In-Person Site or Home Health Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	
Pregnancy test (β-hCG)	X						X	X	• A negative urine pregnancy test must be confirmed at screening and prior to dispensing treatment for all WOCBP. 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 ±3 or ET visit. • Local urine testing (ie, at the site, home, etc) will be standard for the protocol unless serum testing is required by local regulation or IRB/EC or the participant is anuric. • See Section 8.3.5, Appendix 2 and Appendix 4.
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 and Appendix 9.
Rapid antigen testing	X								• Only required if a participant does not have results of a positive SARS-CoV-2 test that was obtained within 5 days prior treatment assignment. • See Section 5.1.
CCI [redacted]									

Visit Identifier	Screening	Baseline (Day 1)	Day 5	Day 10	Day 14	Day 21	Day 34	ET	Notes
Visit Window	**Day -1 to Day 1**	**0 days**	**0 days**	**±1 day**	**±2 days**	**±2 days**	**±3 days**		
Type of Visit	**In-Person Site or Home Health Visit with Telehealth**	**In-Person Site Visit**	**In-Person Site or Home Health Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	
									CCI [redacted]
Specified biomarker research (plasma)		X	X		[X]		[X]	[X]	• Samples will be collected at Day 1 and Day 5 for all participants. • If an in-person (site or home health) visit is conducted, this sample should be collected at Day 14 ±2 days, Day 34 ±3 days and ET visits. • See Section 8.7.2.1.
Retained Research Samples for biomarkers (Prep B2.5)		X	X		[X]		[X]	[X]	• Samples will be collected at Day 1 and Day 5 for all participants. • See Section 8.7.3. • If an in-person (site or home health) visit is conducted, this sample should be collected at Day 14 ±2 days, Day 34 ±3 days or ET visits.
Retained research samples for genetics (Prep D1)		X							• Prep D1 Retained Research Samples for Genetics: 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.
PHARMACOKINETICS									
Tasso M20 Device Training	X								• For Tasso collection, the site staff should confirm and document in the source that the participant (and/or caregivers) receives training on sample collection and can collect a sample for training purposes only at Screening. • Eligibility should be assessed against available information prior to conducting Tasso Training. See Section 8.1.

Visit Identifier	Screening	Baseline (Day 1)	Day 5	Day 10	Day 14	Day 21	Day 34	ET	Notes
Visit Window	**Day -1 to Day 1**	**0 days**	**0 days**	**±1 day**	**±2 days**	**±2 days**	**±3 days**		
Type of Visit	**In-Person Site or Home Health Visit with Telehealth**	**In-Person Site Visit**	**In-Person Site or Home Health Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	
									• The participant (and/or caregiver) should demonstrate proficiency with Tasso collection. If the participant has not yet shown proficiency at screening during a training Tasso collection, the Day 1 required Tasso PK sample collection needs to be observed in-clinic. • Site should consider contacting the participant (and/or caregiver) for the first time a Tasso sample collection is performed at home, via a telehealth visit. • See Section 8.5.
For participants not on HD (Cohort 1): PK sample collected at in-person visits or collected using Tasso device		X (See PK schema)							• Cohort 1: See PK sampling schema for participants with severe renal impairment not on HD (Cohort 1). • The Tasso PK and and venous blood (split venous blood sample into 2 aliquotes; whole blood and plasma) will be collected on-site (investigational site or home health visit)) for PK analyses as per the PK Sampling Schema. • See PK schema below and Section 8.5.
For participants on HD (Cohort 2): PK sample collected at in-person visits, at dialysis (venous) or collected using Tasso device		X (See PK schema)							• See PK sampling schema for participants with severe renal impairment on HD (Cohort 2). • The Tasso PK and venous blood (split venous blood sample into 2 aliquotes; whole blood and plasma) will be collected on-site (investigational site or HD center) for PK analyses as per the PK Sampling Schemas. • See PK schemas below and Section 8.5.
TREATMENT ASSIGNMENT		X							• Participants will be assigned treatment using an IRT system.

Visit Identifier	Screening	Baseline (Day 1)	Day 5	Day 10	Day 14	Day 21	Day 34	ET	Notes
Visit Window	**Day -1 to Day 1**	**0 days**	**0 days**	**±1 day**	**±2 days**	**±2 days**	**±3 days**		
Type of Visit	**In-Person Site or Home Health Visit with Telehealth**	**In-Person Site Visit**	**In-Person Site or Home Health Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	
									• See Section 6.3.
STUDY INTERVENTION									

Study intervention administration		Day 1 through Day 5 (5 doses total)							• All participants take 2 tablets of PF-07321332 (nirmatrelvir) and 1 capsule of ritonavir (300 mg/100 mg) on Day 1. On Days 2-5, take 1 tablet of PF-07321332 (nirmatrelvir) and 1 capsule of ritonavir (150 mg/100 mg) daily. Take the tablet and capsule approximately 10 minutes or less apart, if feasible, but no more than 15 minutes apart.
									• For non-HD pts (Cohort 1):
									  • Participants should take the first dose of study intervention on Day 1 during the in-clinic visit.
									  • The participant selects a once daily dosing time for Days 2-5. Day 2 dose should be taken no earlier than 14 hours and no later than 28 hours after the Day 1 dose.
									  • The remaining doses (Days 3-5) should be taken at approximately the same time (±4 hours) as the Day 2 dose.
									• For HD participants (Cohort 2):
									  • **If Day 1 dose is taken on a non-HD day:**
									  o Participants should take the Day 1 dose of study intervention during the in-clinic visit.
									  o For Days 2-5, the participant selects a once daily dosing

Visit Identifier	Screening	Baseline (Day 1)	Day 5	Day 10	Day 14	Day 21	Day 34	ET	Notes
Visit Window	**Day -1 to Day 1**	**0 days**	**0 days**	**±1 day**	**±2 days**	**±2 days**	**±3 days**		
Type of Visit	**In-Person Site or Home Health Visit with Telehealth**	**In-Person Site Visit**	**In-Person Site or Home Health Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	
									time that would be after HD. Day 2 dose should be taken no earlier than 14 hours and no later than 28 hours after the Day 1 dose. o The remaining doses (Days 3-5) should be taken at approximately the same time (±4 hours) as the Day 2 dose. • **If Day 1 dose is taken on an HD day:** o Participants should take the Day 1 dose of study intervention in the clinic after HD. o On study Day 2, the participant selects a once daily dosing time that would be after the typical time the participant would complete HD on HD days. Day 2 dose should be taken no earlier than 14 hours and no later than 28 hours after the Day 1 dose. o The remaining doses (Days 3-5) should be taken at approximately the same time (±4 hours) as the Day 2 dose. • See Section 6.1.

Visit Identifier	Screening	Baseline (Day 1)	Day 5	Day 10	Day 14	Day 21	Day 34	ET	Notes
Visit Window	**Day -1 to Day 1**	**0 days**	**0 days**	**±1 day**	**±2 days**	**±2 days**	**±3 days**		
Type of Visit	**In-Person Site or Home Health Visit with Telehealth**	**In-Person Site Visit**	**In-Person Site or Home Health Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	
STUDY PROCEDURES									
Collect/update secondary contacts	X	X							• The investigator will capture contact information for at least 2 individuals who the site can contact if the participant is unable to be reached after multiple attempts.
Record COVID-19-related medical visits (Hospitalization and ER visit)			X	X	X	X	X	X	• COVID-19 related hospitalizations and emergency department visits which have occurred since the last assessment will be collected. • See Section 8.2.1.
Vital Status Check							X	X	• Record the vital status (whether the participant is alive or dead) in the appropriate CRF. • See Section 7.2.1.
Study kit dispensed and participant instructed on its use		X							• The study kit includes documents and materials that will facilitate participant completion of at-home study procedures.
Participant-completed electronic diary (study intervention log)		Day 1 through Day 5							• The electronic diary will be provided or application downloaded to participant's own device and training completed at the Baseline visit. • Daily dosing will be entered in an electronic diary Days 1 through Day 5. The Day 1 dose at the site should be entered in the eDiary by the participant (or caregiver) while on site. • For participants who are using an eDiary provided through the study, the eDiary will be collected on Day 5, the next scheduled visit or ET visit after completion of dosing log entries on the device.

Visit Identifier	Screening	Baseline (Day 1)	Day 5	Day 10	Day 14	Day 21	Day 34	ET	Notes
Visit Window	**Day -1 to Day 1**	**0 days**	**0 days**	**±1 day**	**±2 days**	**±2 days**	**±3 days**		
Type of Visit	**In-Person Site or Home Health Visit with Telehealth**	**In-Person Site Visit**	**In-Person Site or Home Health Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	
Investigational Site check of participant eDiary dosing entries		Day 1 through Day 5							• On Days 1-5, site personnel will review eDiary participant dosing entries daily on the Trial Manager portal and contact participant if not completed. • See Section 6.5.
Record HD Details (Cohort 2 only)		HD Days during Day 1 through Day 5							• During HD treatment, site staff should record relevant HD details on the designated CRF.
Retrieval of unused study intervention and empty study intervention containers			X		[X]			[X]	• If the Day 5 visit is conducted prior to last dose of study intervention on Day 5, empty study intervention containers, and unused study intervention should be returned at the next in-person visit (Day 14). The electronic diary should be reviewed and device should be returned if applicable. • See Section 6.5.
Study intervention accountability			X		[X]			[X]	• Study intervention accountability should be performed at Day 5 visit. If Day 5 visit is prior to last dose of study intervention on Day 5, study intervention accountability can be performed at the next in-person visit (Day 14). • See Section 6.2.
Contraception check	X	X	X	X	X	X	X	X	• See Section 5.3.1.
Prior/concomitant medications	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. • Concomitant therapies will be collected through the Day 34 visit. • See Section 6.9.

Visit Identifier	Screening	Baseline (Day 1)	Day 5	Day 10	Day 14	Day 21	Day 34	ET	Notes
Visit Window	**Day -1 to Day 1**	**0 days**	**0 days**	**±1 day**	**±2 days**	**±2 days**	**±3 days**		
Type of Visit	**In-Person Site or Home Health Visit with Telehealth**	**In-Person Site Visit**	**In-Person Site or Home Health Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	**In-Person Site, Home Health or Telehealth Visit**	
Adjunctive therapeutic procedures	X	X	X	X	X	X	X	X	• Non-drug treatments and procedures will be collected through the Day 34 visit.
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	• AEs should be assessed by means of a telehealth visit if not feasible via an in-person visit. See Section 8.1.3. • See Section 8.4.

- Screening: Assessments indicated in brackets [X] will be performed only if needed to confirm eligibility.
- Day 1- Day 34: Assessments indicated in brackets [X] will be performed for in-person (in-clinic or home health) visits and if required per the SoA.
- **Day 10** and **Day 21** visits will be conducted by telehealth. Telehealth visits may be an in-person visit at the discretion of the investigator.
- Day 34 visit may be conducted by telehealth if no in-person procedures need to be performed.
- ET visit may be conducted by telehealth if no in-person procedures need to be performed or if a participant no longer wants to complete an in-person visit.
- All efforts should be made to collect the PK sample on the day of study as designated in the PK schema for participants not on HD and for participants on HD. The visit windows listed in the SoA do not apply to the PK sample collection timepoints. Visit windows are applicable for study procedures (except PK sample collection).

PK SAMPLING SCHEMA 1 – COHORT 1: Severe Renal Impairment not on HD

Study Day	1	2	3	4		5		
PF-07321332 (nirmatrelvir)/ritonavir administration	X	X	X	X		X[a]		
Hours after dose[b]	**1- 3**	**4 -8**	**9 to 15**	**0**	**1 – 4**	**0**	**0.5-6**	**9 to 15**
PK blood sampling (Tasso)	X[c]	X[c]	X[c]	X[d]	X[c]	X[d]	X[c]	X[c]
Blood:Plasma Ratio sample (venous)	X[e]		[X[e]]	[X[e]]		[X[e]]		

a. For Day 5 in-person (site or home health) visit:
   - If the time of the scheduled visit is within the dosing window (± 4 hours), participants should wait to take the dose of PF-07321332 (nirmatrelvir)/ritonavir during the in-person visit. The dose will be taken after the pre-dose PK sample has been obtained and thereafter PK samples will be obtained according to the PK timepoint schedule;
   - If the time of the scheduled visit is not within the dosing window (± 4 hours), participants should take the dose of PF-07321332 (nirmatrelvir)/ritonavir at the participant's usual time and PK samples will be obtained according to the PK timepoint schedule.

b. Hours are in reference to the QD dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.

c. Tasso blood sample: After dosing study drug, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).

d. Tasso blood sample: Prior to dosing study drug, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).

e. Blood:Plasma Ratio venous sample: Collect immediately before or after the Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect first sample on Day 1 and second sample either on Day 3 or Day 4 or Day 5. It is advised to have second sample collected on Day 5, given the need for in-person visit.

PK SAMPLING SCHEMA 2 – COHORT 2: HD cohort with 1st Dose on HD day that is Monday

Study Day	Day 1 – HD MONDAY	Day 2 – no HD TUESDAY	Day 3 – HD WEDNESDAY	Day 4 – no HD THURSDAY				Day 5 – HD FRIDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X[b]	X	X[b]	X				X[b]
Hours after dose[a]	**1 – 3**		**Before and During HD**	**0**	**0.5 – 3**	**4 – 8**	**9 – 15**	**Before HD start**
PK blood sampling (Tasso)	X[f]		X[c]	X[c]	X[f]	X[f]	X[f]	[X[c]]
PK blood sampling during HD (arterial and venous ports)			X[d]					X[e]
Hematology blood sample (hematocrit)			X[i]					
Blood:Plasma Ratio sample (venous)	X[h]		X[g, h]	[X[h]]				[X[g, h]]

a. Hours are in reference to the QD dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants will take study intervention as soon as feasible after HD.
c. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
d. Venous blood samples: HD staff to obtain PK blood samples from the HD filter arterial port and the venous port at 0 hr (prior to start of HD) and at 0.5, 1, 2, 3, and 4 hours post start of dialysis.
e. Day 5 PK blood sample: If participant goes to HD treatment prior to going to investigational site on Day 5, then HD staff to obtain this venous sample prior to the start of dialysis from the venous HD line. If participant goes to investigational site prior to going to HD on Day 5, then investigational site staff can obtain PK sample using the Tasso device.
f. Tasso blood samples: After dosing study drug, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). Collect the consecutive PK samples within the prescribed windows with each sample taken a minimum of 2 hours apart.
g. Blood:Plasma Ratio venous sample: Collect at 0 hr prior to start of HD.
h. Blood:Plasma Ratio venous sample: Collect immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 3. If one sample is missed, it may be collected on Day 4 or Day 5. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
i. Hematocrit: Obtain 2 hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

PK SAMPLING SCHEMA 3 - COHORT 2: HD cohort with 1st Dose on HD day that is Tuesday

Study Day	Day 1 – HD TUESDAY	Day 2 - no HD WEDNESDAY	Day 3 - HD THURSDAY	Day 4 - no HD FRIDAY				Day 5 - HD SATURDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X[b]	X	X[b]	X				X[b]
Hours after dose[a]	**1 – 3**		**Before and During HD**	**0**	**0.5 - 3**	**4 - 8**	**9 - 15**	**Before HD start**
PK blood sampling (Tasso)	X[f]		X[c]	X[c]	X[f]	X[f]	X[f]	[X[c]]
PK blood sampling during HD (arterial and venous ports)			X[d]					X[e]
Hematology blood sample (hematocrit)			X[i]					
Blood:Plasma Ratio sample (venous)	X[h]		X[g, h]	[X[h]]				[X[g, h]]

a. Hours are in reference to the dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants will take study intervention as soon as feasible after HD.
c. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
d. Venous blood samples: HD staff to obtain PK blood samples from the HD filter arterial port and the venous port at 0 hr (prior to start of HD) and at 0.5, 1, 2, 3, and 4 hours post start of dialysis.
e. Day 5 PK blood sample: If participant goes to HD treatment prior to going to investigational site on Day 5, then HD staff to obtain this venous sample prior to the start of dialysis from the venous HD line. If participant goes to investigational site prior to going to HD on Day 5, then investigational site staff can obtain PK sample using the Tasso device.
f. Tasso blood samples: After dosing study drug, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). On Day 4, collect the consecutive PK samples within the prescribed windows with each sample taken a minimum of 2 hours apart.
g. Blood:Plasma Ratio venous sample: Collect at 0 hr prior to start of HD.
h. Blood:Plasma Ratio venous sample: Collect immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 3. If one sample is missed, it may be collected on Day 4 or Day 5. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
i. Hematocrit: Obtain two hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

PK SAMPLING SCHEMA 4 - COHORT 2: HD cohort with 1st Dose on HD day that is Wednesday

Study Day	Day 1 – HD WEDNESDAY	Day 2 - no HD THURSDAY	Day 3 - HD FRIDAY	Day 4 - no HD SATURDAY				Day 5 - no HD SUNDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X[b]	X	X[b]	X				X[c]
Hours after dose[a]	**1 - 3**		**Before and During HD**	**0**	**0.5 - 3**	**4 - 8**	**9 - 15**	**0**
PK blood sample (Tasso)	X[f]		X[d]	X[d]	X[f]	X[f]	X[f]	X[c, d]
PK blood sampling during HD (arterial and venous ports)			X[e]					
Hematology blood sample (hematocrit)			X[i]					
Blood:Plasma Ratio sample (venous)	X[h]		X[g, h]	[X[h]]				[X[h]]

a. Hours are in reference to the dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants will take study intervention as soon as feasible after HD.
c. For the Day 5-in-person visit, 1) if the time of the scheduled visit is within the dosing window (± 4 hours), participants should wait to take the dose of PF-07321332 (nirmatrelvir)/ritonavir until the in-person visit. The dose will be taken after the pre-dose PK sample has been obtained; 2). If the time of the scheduled visit is not within the dosing window (± 4 hours), participants should take the dose of PF-07321332 (nirmatrelvir)/ritonavir at the participant's usual time and PK samples taken per the schedule.
d. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
e. Venous blood samples: HD staff to obtain PK blood samples from the HD filter arterial port and the venous port at 0 hr (prior to start of HD) and at 0.5, 1, 2, 3, and 4 hours post start of dialysis.
f. Tasso blood samples: After dosing study drug, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). On Day 4, collect the consecutive PK samples within the prescribed windows with each sample taken a minimum of 2 hours apart.
g. Blood:Plasma Ratio venous sample: Collect at 0 hr prior to start of HD.
h. Blood:Plasma Ratio venous sample: Collect immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 3. If one sample is missed, it may be collected on Day 4 or Day 5. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
i. Hematocrit: Obtain 2 hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

PK SAMPLING SCHEMA 5 - COHORT 2: HD cohort with 1st Dose on HD day that is Thursday

Study Day	Day 1 – HD THURSDAY	Day 2 - no HD FRIDAY	Day 3 - HD SATURDAY	Day 4 - no HD SUNDAY				Day 5 - no HD MONDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X[b]	X	X[b]	X				X[c]
Hours after dose[a]	**1 - 3**		**Before and During HD**	**0**	**0.5 - 3**	**4 - 8**	**9 - 15**	**0**
PK blood sample (Tasso)	X[f]		X[d]	X[d]	X[f]	X[f]	X[f]	X[d, h]
PK blood sampling during HD (arterial and venous ports)			X[e]					
Hematology blood sample (hematocrit)			X[i]					
Blood:Plasma Ratio sample (venous)	X[h]		X[g,h]	[X[h]]				[X[h]]

a. Hours are in reference to the dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants will take study intervention as soon as feasible after HD.
c. For the Day 5-in-person visit, 1) if the time of the scheduled visit is within the dosing window (± 4 hours), participants should wait to take the dose of PF-07321332 (nirmatrelvir)/ritonavir until the in-person visit. The dose will be taken after the pre-dose PK sample has been obtained; 2). If the time of the scheduled visit is not within the dosing window (± 4 hours), participants should take the dose of PF-07321332 (nirmatrelvir)/ritonavir at the participant's usual time and PK samples taken per the schedule.
d. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
e. Venous blood samples: HD staff to obtain PK blood samples from the HD filter arterial port and the venous port at 0 hr (prior to start of HD) and at 0.5, 1, 2, 3, and 4 hours post start of dialysis.
f. Tasso blood samples: After dosing study drug, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). On Day 4, collect the consecutive PK samples within the prescribed windows with each sample taken a minimum of 2 hours apart.
g. Blood:Plasma Ratio venous sample: Collected at 0 hr prior to start of HD.
h. Blood:Plasma Ratio venous sample: Collected immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 3. If one sample is missed, it may be collected on Day 4 or Day 5. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
i. Hematocrit: Obtain 2 hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

PK SAMPLING SCHEMA 6 - COHORT 2: HD cohort with 1st Dose on HD day that is Friday

Study Day	Day 1 – HD FRIDAY	Day 2 - no HD SATURDAY	Day 3 - no HD SUNDAY				Day 4 - HD MONDAY	Day 5 - no HD TUESDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X[b]	X	X				X[b]	X[c]
Hours after dose[a]	**1 - 3**		**0**	**0.5 - 3**	**4 - 8**	**9-15**	**Before and During HD**	**0**
PK blood sampling (Tasso)	X[e]		X[d]	X[e]	X[e]	X[e]	X[d]	X[d]
PK blood sampling during HD (arterial and venous ports)							X[f]	
Hematology blood sample (hematocrit)							X[i]	
Blood:Plasma Ratio sample (venous)	X[h]		[X[h]]				X[g, h]	[X[h]]

a. Hours are in reference to the dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants should take the dose of study intervention as soon as feasible after HD.
c. For the Day 5 in-person visit, 1) if the time of the scheduled visit is within the dosing window (± 4 hours), participants should wait to take the dose of PF-07321332 (nirmatrelvir)/ritonavir until the in-person visit. The dose will be taken after the pre-dose PK sample has been obtained; 2). If the time of the scheduled visit is not within the dosing window (± 4 hours), participants should take the dose of PF-07321332 (nirmatrelvir)/ritonavir at the participant's usual time and PK samples taken per the schedule.
d. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
e. Tasso blood samples: After dosing study drug, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). Collect the consecutive PK samples within the prescribed windows and with each sample a minimum of 2 hours apart.
f. Venous blood samples: HD staff to obtain PK blood samples from the HD filter arterial port and venous port at 0 hr (prior to start of HD) and at 0.5, 1, 2, 3, and 4 hours post start of dialysis.
g. Blood:Plasma Ratio venous sample: Collected at 0 hr prior to start of HD
h. Blood:Plasma Ratio venous sample: Collected immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 4. If one sample is missed, it may be collected on Day 3 or Day 5. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
i. Hematocrit: Obtain 2 hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

PK SAMPLING SCHEMA 7 - COHORT 2: HD cohort with 1st Dose on HD day that is Saturday

Study Day	Day 1 – HD SATURDAY	Day 2 - no HD SUNDAY	Day 3 - no HD MONDAY				Day 4 - HD TUESDAY	Day 5 - no HD WEDNESDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X[b]	X	X				X[b]	X[c]
Hours after dose[a]	**1 - 3**		**0**	**0.5 - 3**	**4 - 8**	**9-15**	**Before and During HD**	**0**
PK blood sampling (Tasso)	X[e]		X[d]	X[e]	X[e]	X[e]	X[d]	X[d]
PK blood sampling during HD (arterial and venous ports)							X[f]	
Hematology blood sample (hematocrit)							X[i]	
Blood:Plasma Ratio sample (venous)	X[h]		[X[h]]				X[g, h]	[X[h]]

a. Hours are in reference to the dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants should take the dose of study intervention as soon as feasible after HD.
c. For the Day 5 in-person visit, 1) if the time of the scheduled visit is within the dosing window (± 4 hours), participants should wait to take the dose of PF-07321332 (nirmatrelvir)/ritonavir until the in-person visit. The dose will be taken after the pre-dose PK sample has been obtained; 2). If the time of the scheduled visit is not within the dosing window (± 4 hours), participants should take the dose of PF-07321332 (nirmatrelvir)/ritonavir at the participant's usual time and PK samples taken per the schedule.
d. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
e. Tasso blood samples: After dosing study drug, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). Collect the consecutive PK samples within the prescribed windows with each sample taken a minimum of 2 hours apart.
f. Venous blood samples: HD staff to obtain PK blood samples from the HD filter arterial port and venous port at 0 hr (prior to start of HD) and at 0.5, 1, 2, 3, and 4 hours post start of dialysis.
g. Blood:Plasma Ratio venous sample: Collected at 0 hr prior to start of HD.
h. Blood:Plasma Ratio venous sample: Collected immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 4. If one sample is missed, it may be collected on Day 3 or Day 5. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
i. Hematocrit: Obtain 2 hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

PK SAMPLING SCHEMA 8 - COHORT 2: HD cohort with 1st Dose on non-HD day Monday

Study Day	Day 1 - no HD MONDAY	Day 2 – HD TUESDAY	Day 3 – no HD WEDNESDAY				Day 4 – HD THURSDAY	Day 5 - no HD FRIDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X	X[b]	X				X[b]	X[h]
Hours after dose[a]	**1 - 3**	**At end of HD (prior to dosing)**	**0**	**0.5 - 3**	**4 - 8**	**9 - 15**	**Before and during HD**	**0**
PK blood sampling (Tasso)	X[e]	[X[d]]	X[d]	X[e]	X[e]	X[e]	X[d]	X[d]
PK blood sampling during HD (arterial and venous ports)							X[c]	
Hematology blood sample (hematocrit)							X[i]	
Blood:Plasma Ratio sample (venous)	X[g]	[X[g]]	[X[g]]				X[f, g]	[X[g]]

a. Hours are in reference to the dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants will take study intervention as soon as feasible after HD.
c. Venous blood samples: HD staff to obtain PK blood samples from the HD filter arterial port and the venous port at 0 hr (prior to start of HD) and at 0, 0.5, 1, 2, 3, and 4 hours post start of dialysis.
d. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
e. Tasso blood samples: After dosing, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). Collect the consecutive PK samples within the prescribed windows with each sample taken a minimum of 2 hours apart.
f. Blood:Plasma Ratio venous sample: Collected at 0 hr prior to start of HD
g. Blood:Plasma Ratio venous sample: Collected immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 4. If one sample is missed, it may be collected on Day 2, Day 3 or Day 5. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
h. For the Day 5 in-person visit, 1) If the time of the scheduled visit is within the dosing window (± 4 hours), participants should wait to take the dose of PF-07321332 (nirmatrelvir)/ritonavir until the in-person visit. The dose will be taken after the pre-dose PK sample has been obtained; 2). If the time of the scheduled visit is not within the dosing window (± 4 hours), participants should take the dose of PF-07321332 (nirmatrelvir)/ritonavir at the participant's usual time and PK samples taken per the schedule.
i. Hematocrit: Obtain 2 hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

PK SAMPLING SCHEMA 9 - COHORT 2: HD cohort with 1st Dose on non-HD day Tuesday

Study Day	Day 1 - no HD TUESDAY	Day 2 – HD WEDNESDAY	Day 3 – no HD THURSDAY				Day 4 – HD FRIDAY	Day 5 - no HD SATURDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X	X[b]	X				X[b]	X[h]
Hours after dose[a]	**1 - 3**	**At end of HD (prior to dosing)**	**0**	**0.5 - 3**	**4 - 8**	**9 - 15**	**Before and During HD**	**0**
PK blood sampling (Tasso)	X[e]	[X[d]]	X[d]	X[e]	X[e]	X[e]	X[d]	X[d]
PK blood sampling during HD (arterial and venous ports)							X[c]	
Hematology blood sample (hematocrit)							X[i]	
Blood:Plasma Ratio sample (venous)	X[g]	[X[g]]	[X[g]]				X[f, g]	[X[g]]

a. Hours are in reference to the dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants will take study intervention as soon as feasible after HD.
c. Venous blood samples: HD staff to obtain PK blood samples from the HD filter arterial port and the venous port at 0 hr (prior to start of HD) and at 0, 0.5, 1, 2, 3, and 4 hours post start of dialysis.
d. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
e. Tasso blood samples: After dosing, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). Collect the consecutive PK samples within the prescribed windows with each sample taken a minimum of 2 hours apart.
f. Blood:Plasma Ratio venous sample: Collected at 0 hr prior to start of HD.
g. Blood:Plasma Ratio venous sample: Collected immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 4. If one sample is missed, it may be collected on Day 2, Day 3 or Day 5. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
h. For the Day 5 in-person visit, 1) If the time of the scheduled visit is within the dosing window (± 4 hours), participants should wait to take the dose of PF-07321332 (nirmatrelvir)/ritonavir until the in-person visit. The dose will be taken after the pre-dose PK sample has been obtained; 2). If the time of the scheduled visit is not within the dosing window (± 4 hours), participants should take the dose of PF-07321332 (nirmatrelvir)/ritonavir at the participant's usual time and PK samples taken per the schedule.
i. Hematocrit: Obtain 2 hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

PK SAMPLING SCHEMA 10 - COHORT 2: HD cohort with 1st Dose on non-HD day Wednesday

Study Day	Day 1 – no HD WEDNESDAY	Day 2 – HD THURSDAY	Day 3 – no HD FRIDAY				Day 4 - HD SATURDAY	Day 5 - no HD SUNDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X	X[b]	X				X[b]	X[h]
Hours after dose[a]	**1 – 3**	**At end of HD (prior to dosing)**	**0**	**0.5 – 3**	**4 – 8**	**9 – 15**	**Before and During HD**	**0**
PK blood sampling (Tasso)	X[e]	[X[d]]	X[d]	X[e]	X[e]	X[e]	X[d]	X[d]
PK blood sampling during HD (arterial and venous ports)							X[c]	
Hematology blood sample (hematocrit)							X[i]	
Blood:Plasma Ratio sample (venous)	X[g]	[X[g]]	[X[g]]				X[f, g]	[X[g]]

a. Hours are in reference to the dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants will take study intervention as soon as feasible after HD.
c. Venous blood samples: HD staff to obtain PK blood samples from the HD filter arterial port and the venous port at 0 hr (prior to start of HD) and at 0, 0.5, 1, 2, 3, and 4 hours post start of dialysis.
d. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
e. Tasso blood samples: After dosing, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). Collect the consecutive PK samples within the prescribed windows with each sample taken a minimum of 2 hours apart.
f. Blood:Plasma Ratio venous sample: Collected at 0 hr prior to start of HD
g. Blood:Plasma Ratio venous sample: Collected immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 4. If one sample is missed, it may be collected on Day 2, Day 3 or Day 5. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
h. For the Day 5 in-person visit, 1) If the time of the scheduled visit is within the dosing window (± 4 hours), participants should wait to take the dose of PF-07321332 (nirmatrelvir)/ritonavir until the in-person visit. The dose will be taken after the pre-dose PK sample has been obtained; 2). If the time of the scheduled visit is not within the dosing window (± 4 hours), participants should take the dose of PF-07321332 (nirmatrelvir)/ritonavir at the participant's usual time and PK samples taken per the schedule.
i. Hematocrit: Obtain 2 hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

PK SAMPLING SCHEMA 11 - COHORT 2: HD cohort with 1st Dose on non-HD day Thursday

Study Day	Day 1 - no HD THURSDAY	Day 2 – HD FRIDAY	Day 3 – no HD SATURDAY				Day 4 - no HD SUNDAY	Day 5 – HD MONDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X	X[b]	X				X	X[b]
Hours after dose[a]	**1 - 3**	**At end of HD (prior to dosing)**	**0**	**0.5 - 3**	**4 - 8**	**9 - 15**	**0**	**Before and During HD**
PK blood sampling (Tasso)	X[e]	[X[d]]	X[d]	X[e]	X[e]	X[e]	X[d]	X[d]
PK blood sampling during HD (arterial and venous ports)								X[c]
Hematology blood sample (hematocrit)								X[i]
Blood:Plasma Ratio sample (venous)	X[h]	[X[h]]	[X[h]]				[X[h]]	X[g, h]

a. Hours are in reference to the dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants will take study intervention as soon as feasible after HD.
c. Venous blood samples: HD staff to obtain PK blood samples from theHD filter arterial port and the venous port at 0 hr (prior to start of HD) and at 0, 0.5, 1, 2, 3, and 4 hours post start of dialysis.
d. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
e. Tasso blood samples: After dosing, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). Collect the consecutive PK samples within the prescribed windows with each sample taken a minimum of 2 hours apart.
f. Venous blood sample: at end of HD prior to dosing, one sample will be drawn from the venous port.
g. Blood:Plasma Ratio venous sample: Collected at 0 hr prior to start of HD.
h. Blood:Plasma Ratio venous sample: Collected immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 5. If one sample is missed, it may be collected on Day 2, Day 3 or Day 4. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
i. Hematocrit: Obtain 2 hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

PK SAMPLING SCHEMA 12 - COHORT 2: HD cohort with 1st Dose on non-HD day Friday

Study Day	Day 1 - no HD FRIDAY	Day 2 – HD SATURDAY	Day 3 - no HD SUNDAY				Day 4 - no HD MONDAY	Day 5 - HD TUESDAY
PF-07321332 (nirmatrelvir)/ritonavir administration	X	X[b]	X				X	X[b]
Hours after dose[a]	**1 - 3**	**At end of HD (prior to dosing)**	**0**	**0.5 - 3**	**4 - 8**	**9 - 15**	**0**	**Before and During HD**
PK blood sampling (Tasso)	X[e]	[X[d]]	X[d]	X[e]	X[e]	X[e]	X[d]	X[d]
PK blood sampling during HD (arterial and venous ports)								X[c]
Hematology blood sample (hematocrit)								X[h]
Blood:Plasma Ratio sample (venous)	X[g]	[X[g]]	[X[g]]				[X[g]]	X[f, g]

a. Hours are in reference to the dose of PF-07321332 (nirmatrelvir)/ritonavir on each study day. The Day 1 dose should be taken at the clinic visit.
b. On dialysis days, participants will take study intervention as soon as feasible after HD.
c. Venous blood samples: HD staff to obtain PK blood samples from the HD filter arterial port and the venous port at 0 hr (prior to start of HD) and at 0, 0.5, 1, 2, 3, and 4 hours post start of dialysis.
d. Tasso blood sample: Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate).
e. Tasso blood samples: After dosing, Tasso device placed by participant, caregiver, home health provider, or other healthcare provider (as appropriate). Collect the consecutive PK samples within the prescribed windows with each sample taken a minimum of 2 hours apart.
f. Blood:Plasma Ratio venous sample: Collected at 0 hr prior to start of HD.
g. Blood:Plasma Ratio venous sample: Collected immediately before or after a Tasso sample but no longer than 15 minutes between the samples. The blood:plasma ratio sample tube is divided into 1 blood sample (in a cryovial) and, after centrifugation, 1 plasma sample (in another cryovial) (reference the Central Lab Manual). Collect blood:plasma ratio samples on Day 1 and Day 5. If one sample is missed, it may be collected on Day 2, Day 3 or Day 4. Always collect a corresponding Tasso sample for each blood:plasma ratio sample.
h. Hematocrit: Obtain 2 hematology blood samples (hematocrit) - one at time 0 hr (venous port sample) and one time of the last PK draw (venous port sample) during HD (hematocrit needed for CLd calculations).

2. INTRODUCTION

PF-07321332 (nirmatrelvir), an orally administered potent and selective SARS-CoV-2 M^{pro} inhibitor, is currently being investigated in participants with COVID-19 and severe renal impairment.

2.1. Study Rationale

The purpose of this study is to evaluate the safety and PK of PF-07321332 (nirmatrelvir)/ritonavir for the treatment of adult participants with COVID-19 with severe renal impairment not on HD and on HD.

The safety and efficacy of PF-07321332 (nirmatrelvir)/ritonavir in adults was demonstrated in Study C4671005 (EPIC-HR, NCT04960202), which enrolled non-hospitalized symptomatic adults with confirmed COVID-19 with at least one risk factor for progression to severe disease. Participants who received PF-07321332 (nirmatrelvir)/ritonavir within 5 days of symptom onset had an 88% (95% CI: 75%, 94%) reduction in risk of COVID-19 related hospitalization or death.

On 22 December 2021, the US FDA granted Emergency Use Authorization to PF-07321332 (nirmatrelvir) co-packaged with 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 use of PF-07321332 (nirmatrelvir)/ritonavir is presently not recommended in adults with severe renal impairment due to a lack of data in this population.[2] The safety and pharmacokinetics of PF-07321332 (nirmatrelvir) has not been studied in adult participants with COVID-19 who require HD and there is limited available data in renal impairment not on HD.

2.2. Background

In December 2019, COVID-19 was identified as a new, potentially fatal, respiratory infection caused by the novel coronavirus, SARS-CoV-2. The WHO declared COVID-19 a Public Health Emergency of International Concern on 30 January 2020 and further characterized the disease outbreak as a pandemic on 11 March 2020.[3] As of 22 June 2022, at least 540 million cases have been confirmed worldwide, and at least 6.3 million deaths have occurred.[4]

COVID-19 manifests as a wide range of illness, from asymptomatic infection to severe pneumonia, ARDS, and death. Although most (approximately 80%) cases are asymptomatic or mild,[5] patients who are hospitalized with COVID-19 may have significant morbidity and mortality[6,7] and are at increased risk of developing complications such as severe inflammation associated with elevations in proinflammatory cytokines, ARDS, acute cardiac injury, thromboembolic events, hypercoagulability, and/or kidney injury.[8-11] Moreover, other comorbidities, such as hypertension, obesity, and diabetes, as well as older age and male sex increase the risk for worse outcomes.[6]

Patients with COVID-19 may have pre-existing renal impairment due to CKD, which is known to have an estimated global prevalence of 8.5–9.8%.[12] Renal impairment and renal replacement therapy are associated with an increased risk of infection due to comorbidities,

uremia, and skin barrier disruptions. Impairment of renal function is independently associated with an increase in susceptibility to SARS-CoV-2 infection and COVID-19 disease and subsequent risk of adverse outcomes.[13] In one large study population-based study in England of over 17 million adults, a history of dialysis or end-stage renal failure was associated with a 3 to 4-fold increase in the risk of death from COVID-19.[13]

There is a high unmet need for effective antiviral agents that can be used in patients with COVID-19 and severe renal impairment who are at high risk of progression to severe disease. Although there are treatments for COVID-19 which are approved under emergency use authorizations, there is limited data on the safety and PK of the treatments in patients with severe renal impairment or on HD.[13-17] Remdesivir, an IV anti-viral with activity against SARS-CoV-2 which is approved[15] for hospitalized and non-hospitalized patients with COVID-19 at high risk of progression to severe COVID-19 or death, is not recommended for patients with eGFR <30 mL/min.[15] Molnupiravir, another anti-viral agent with activity against SARS-CoV-2, has received emergency use authorization from FDA for treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19[17]. The PK of molnupiravir has not been evaluated in patients with end stage renal disease or on dialysis, although a significant effect on exposure is not expected. Molnupiravir reported in the final analysis in 1433 patients with at least one risk factor for progression of COVID-19 showed 6.8% hospitalization or death in the molnupiravir group versus 9.7% in the placebo group (a 31% risk reduction).[17]

Currently there are 2 monoclonal antibody treatments which have received EUA for outpatient use in high-risk patients affected by COVID-19. Bebtelovimab and sotrovimab both have demonstrated activity against the SARS-CoV-2 Omicron variant. Although no clinical trials have been conducted for sotrovimab and bebtelovimab in renally impaired participants, renal impairment is not expected to affect the exposure of both of these agents.[18,19]

PF-07321332 (nirmatrelvir) is a potent and selective inhibitor of the SARS-CoV-2 M^{pro} and is being developed as an oral treatment in patients with COVID-19. An oral antiviral agent would be an easy and convenient method of drug administration without requiring attendance at a healthcare setting. Whereas mAb treatment and remdesivir need to be administered parenterally which will add additional burden on healthcare setting.

This study will provide PK and safety data for PF-07321332 (nirmatrelvir)/ritonavir in participants with severe renal impairment not on HD and on HD. PF-07321332 (nirmatrelvir) is co-administered with ritonavir, a strong CYP3A4 inhibitor, to achieve exposures sufficient to suppress viral replication through the entire dosing interval (ie, C_{trough}>EC_{90}). Ritonavir does not have any antiviral activity against the SARS-CoV-2 virus.

In published case series report of 15 HD patients with COVID-19, PF-07321332 (nirmatrelvir)/ritonavir was found to be well tolerated with no SAEs.[20]

2.2.1. Clinical Overview

C4671005 (NCT04960202), a Phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized symptomatic adult participants with a laboratory-confirmed diagnosis of SARS-CoV-2 infection, included participants 18 years of age and older with at least 1 risk factor for progression to severe disease and with a COVID-19 symptom onset of ≤5 days. The study excluded individuals with a history of prior COVID-19 infection or SARS-CoV-2 vaccination before the Day 34 visit. The primary efficacy endpoint was the proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.

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; 0.7% of participants who received PF-07321332 (nirmatrelvir)/ritonavir were hospitalized through Day 28 following randomization (5 of 697 hospitalized with no deaths), compared to 6.5% of participants who received placebo and were hospitalized or died (44 of 682 hospitalized with 9 subsequent deaths) ($p<0.0001$). In a secondary endpoint, PF-07321332 (nirmatrelvir)/ritonavir reduced the risk of hospitalization or death for any cause by 88% compared with placebo in participants treated within 5 days of symptom onset; 0.8% of patients who received PF-07321332 (nirmatrelvir)/ritonavir were hospitalized or died through Day 28 following randomization (8 of 1039 hospitalized with no deaths) compared with 6.3% of patients who received placebo (66 of 1046 hospitalized with 12 subsequent deaths) ($p < 0.0001$). Treatment with PF-07321332 (nirmatrelvir)/ritonavir was safe and well tolerated.

Study C4671002 (NCT05011513), is a Phase 2/3, randomized, double-blind, placebo controlled study in non-hospitalized symptomatic adults with low risk of progression to severe illness. A prespecified interim analysis of Study C4671002, which included 45% of the trial's planned enrollment, showed that the novel primary endpoint of self-reported, sustained alleviation of all symptoms for 4 consecutive days, for PF-07321332 (nirmatrelvir)/ritonavir compared to placebo, was not met. The key secondary endpoint of COVID-19-related hospitalization or death from any cause through Day 28 was also examined at the interim analysis, showing 0.6% of those who received PF-07321332 (nirmatrelvir)/ritonavir were hospitalized following randomization (2 of 333 hospitalized with no deaths), compared to 2.4% of participants who received placebo and were hospitalized (8 of 329 hospitalized with no deaths).

A Phase 1, open label, 2-part study (C4671011) to investigate the effect of stable mild (eGFR ≥60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min), or severe (eGFR <30 mL/min and not requiring dialysis) renal impairment on the plasma and urine PK, safety, and tolerability of PF-07321332 (nirmatrelvir) has been completed. PF-07321332 (nirmatrelvir) systemic exposure increased with increasing severity of renal impairment.[23]

Following a single 100 mg dose of PF-07321332 (nirmatrelvir) administered orally in combination with ritonavir 100 mg dose given at four scheduled time points relative to the single dose, the adjusted geometric mean (90% CI) AUC_{inf}, test/reference ratios for renal

impairment (test) compared to normal renal function (reference) were 123.8 % (99.6%, 153.9%) for mild renal impairment, 187.4% (148.5%, 236.5%) for moderate renal impairment, and 304.49% (237.6%, 390.2%) for severe renal impairment. Adjusted geometric mean (90% CI) test/reference ratios for C_{max} were 129.78% (101.9%, 165.3%) for mild renal impairment, 138.1% (113.2%, 168.6%) for moderate renal impairment, and 148.0% (111.4%, 196.7%) for severe renal impairment participants. Regression plot of CL/F versus eGFR derived from CKD-EPI equation showed a clear trend of decreasing clearance with a decrease in renal function, with intercept of 1.83 ($P = 0.0009$) and slope of 0.05 ($P < 0.0001$).

PF-07321332 (nirmatrelvir)/ritonavir was generally safe and well-tolerated in both healthy and renally impaired adult participants. The number of all-causality TEAEs were similar between the mild (1 AE), moderate (1 AE) and normal renal function (3 AEs) groups. All AEs in these 3 groups were mild and not considered treatment related. A greater number of participants in the severe renal impairment group experienced TEAEs (17 AEs experienced by 5 participants in the severe renally impaired group). Of these 17 AEs, 4 (dry mouth and dysgeusia) were considered treatment related. There were 3 SAEs occurring in 1 participant in the severe renally impaired group, including 1 SAE of acute kidney injury, which resulted in study withdrawal. None of the AEs or SAEs were considered treatment related in this participant. There were no clinically meaningful laboratory findings or trends observed in this study.

The proposed dose is being developed based on internal analysis of data on file using population PK modeling. This analysis demonstrated the CL was reduced by 1/3. This was based on PK modeling using draft data from renally impaired subjects enrolled in the C467 program which included 4 subjects from Study C4671005. Of note, these participants did not experience significant safety events while on study. The data from PK modeling has supported the use of a reduced dose in severe renal impaired participants with COVID-19.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07321332 (nirmatrelvir)/ritonavir may be found in the PF-07321332 (nirmatrelvir)/ritonavir 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: PF-07321332 (nirmatrelvir)	
Dysgeusia	In Study C4671005, dysgeusia was recorded as an AE by 6% of participants receiving PF-07321332 (nirmatrelvir)/ritonavir compared to <1% of participants receiving placebo	Participants may utilize recommendations to alleviate symptoms of dysgeusia while taking treatment such as peppermint post-dose. Dosing recommendations will be provided to the participant.
Emesis	Sporadic emesis was observed at ≥100 mg/kg/day of PF-07321332 (nirmatrelvir) in the 15-day NHP toxicology study.	AEs will be monitored and participants may receive antiemetics.
Hypertension	Transient increases in systolic, diastolic and mean BP were observed in pre-clinical studies. In Study C4671005 (adults at high risk for severe disease) a small imbalance in hypertension AEs (1% vs <1%) was reported.	Vital signs and all AEs will be monitored in the study.
Study Intervention: Ritonavir		
Gastrointestinal disturbances (including diarrhea, nausea, vomiting, and abdominal pain)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose of 100 mg QD is used in this study. There is a short duration of treatment (5 days). 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. In addition to ongoing review of AEs by the sponsor, an E-DMC will review safety data as described in Section 10.1.5.1.
Rash (most commonly reported as erythematous and maculopapular, followed by pruritic)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs and monitoring through targeted physical exams. If needed therapeutic interventions per SoC may be provided.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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. Fatigue (low energy or tiredness) will be assessed through collection of daily signs and symptoms and will also be assessed through targeted physical examinations when performed during the study visits.
Study Procedures		
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.
Tasso device will be applied only to an upper extremity that does not have a functioning HD access.	There is risk of bleeding, bruising, hematoma formation, and infection in the upper extremity and the upper extremity HD access with Tasso device placement.	Only participants undergoing HD and/or caregivers of participants on HD, who have completed training on proper placement of Tasso device on upper extremities without a functioning HD access will be permitted to apply the Tasso device.

2.3.2. Benefit Assessment

PF-07321332 (nirmatrelvir) has been shown to have SARS-CoV-2 antiviral activity in vitro and in Study C4671005 and is intended to reduce viral titers, thereby reducing the duration and severity of symptoms and the risk of hospitalization and mortality in SARS-CoV-2 infected patients. Participants in Study C4671005 who received PF-07321332 (nirmatrelvir)/ritonavir within 5 days of symptom onset had an 88% (95% CI: 75%, 94%) reduction in risk of COVID-19-related hospitalization or death. On this basis, the potential benefit to individual study participants who receive the study intervention may include a shorter time to clinical recovery, prevention of hospitalization, and a lower probability of progressing to more severe illness or death. The potential benefit of the study is that it may provide a new treatment option for non-hospitalized severe renal impairment patients with COVID-19 who are at risk of progression to severe disease. In the context of the global pandemic public health emergency, this treatment could play an important role in alleviating current pressures on health care systems globally.

2.3.3. Overall Benefit/Risk Conclusion

Considering the current COVID-19 global pandemic and the high burden of both mortality and morbidity and the potential for future epidemic outbreaks, the lack of readily available outpatient treatment options, and the measures taken to minimize risk to participants in this study, the potential risks identified in association with PF-07321332 (nirmatrelvir)/ritonavir are justified by the anticipated benefits that may be afforded to severe renal impairment participants with COVID-19.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To describe the safety and tolerability of PF-07321332 (nirmatrelvir)/ritonavir in adult participants with COVID-19 and severe renal impairment.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	• Not Applicable.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the effect of severe renal impairment on the PK of PF-07321332 (nirmatrelvir) in participants not on HD. • To evaluate the effect of severe renal impairment on the PK of PF-07321332 (nirmatrelvir) in participants on HD.	• Plasma PF-07321332 (nirmatrelvir) PK parameters including C_{max}, CL/F, Vz/F, $AUC_{0\text{-}tau}$, $t_{½}$, and C_{trough} estimated from the population PK model.	• Not Applicable.
• To evaluate the effect of HD on the PK of PF-07321332 (nirmatrelvir).	• HD clearance (CLd) of PF-07321332 (nirmatrelvir). • Fraction of PF-07321332 (nirmatrelvir) dose removed from the body by dialysis (Fd).	• Not Applicable.
CCI [redacted]		

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, multi-center, single arm study in approximately 24 non-hospitalized adult participants with COVID-19 and severe renal impairment and not yet receiving intermittent HD (Cohort 1) and severe renal impairment receiving intermittent HD (Cohort 2). The following Cohorts will be enrolled:

- Cohort 1: Severe renal impairment (defined as eGFR <30 mL/min/1.73 m^2) not on HD and mild-to-moderate COVID-19 disease with confirmed SARS-CoV-2 infection and initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of treatment assignment.

- Cohort 2: Severe renal impairment on HD and mild-to-moderate COVID-19 disease with confirmed SARS-CoV-2 infection and initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of treatment assignment.

All eligible participants will be assigned to receive a single dose of PF-07321332 (nirmatrelvir)/ritonavir 300 mg/100 mg orally on Day 1 followed by PF-07321332 (nirmatrelvir)/ritonavir 150 mg/100 mg QD from Day 2 to Day 5. Single dose PK study (Study C4671011) of PF-07321332 (nirmatrelvir)/ritonavir in mild, moderate, and severe renal impairment showed that the PF-07321332 (nirmatrelvir) exposure is approximately 3-fold higher and CL/F is 67% lower in severe renal impairment participants relative to healthy volunteers. Published literature as well as internal data showed there is minimal to no effect of renal impairment on ritonavir PK.[1, 23,24] Ritonavir 100 mg QD or BID dose has been used for several protease inhibitors (eg, darunavir) with small difference in dose normalized C_{trough} of protease inhibitors. Additionally, the PK of PF-07321332 (nirmatrelvir) with 100 mg QD of ritonavir in severe renal impairment participants is expected to be similar to those of healthy participants taking 100 mg BID of ritonavir. Therefore, the ritonavir dose of 100 mg QD was selected for this study.The total study duration is up to 38 days and includes a 1-to 2-day screening period where participants can be screened on one day and randomized the next day or screened and randomized on the same day. Screening procedures can be performed over two days, but the participant must be randomized by the second day (Day 1) and begin study treatment. Therefore, Screening and Randomization can take no longer than 2 consecutive days. After Screening, the participants takes study intervention for 5 days and completes the safety follow-up period through Day 34. Continued collection of ongoing safety information through SAE resolution will occur as applicable.

For PK assessments in severe renal impairment participants not on HD, sparse PK samples will be collected on Day 1 through 5 of dosing. This should be collected using a Tasso device and a venous blood sample as specified in the SoA.

For PK assessments in severe renal impairment participants on HD, samples will be collected on Days 1 through 5 of dosing with respect to the participant's dialysis sessions during treatment. If at home, this should be collected using a Tasso device or may be done at an in-person visit, unless otherwise specified in the SoA. During HD, venous port (entering dialyzer) and arterial port (exiting the dialyzer) blood samples will be collected at 0, 0.5, 1, 2, 3 and 4 hours post the start of dialysis.

This study will use the program-level 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 for this study.

4.2. Scientific Rationale for Study Design

SARS-CoV-2 is the causative agent of COVID-19. SARS-CoV-2 is an enveloped, positive sense single-stranded RNA virus with a glycoprotein spike on the surface. Cell entry requires binding of the spike protein to the cellular receptor ACE-2 and priming of the spike glycoprotein by the host cell serine protease TMPRSS2.[21]

Given the limited data available in severe renal impairment for COVID-19 treatment options and request by FDA during consideration of the EUA for PF-07321332 (nirmatrelvir)/ritonavir to study PF-07321332 (nirmatrelvir) in this population, the study design is in accordance with available draft FDA guidance and takes into consideration the clinical course of these patients when affected by COVID-19 both on and not on HD.

The study population will be divided into a non-HD cohort and a HD cohort with severe renal impairment with awareness that they may be on several medications to be used with caution when taken in conjunction with PF-07321332 (nirmatrelvir)/ritonavir. Therefore, the prohibited medications will be limited to those that are contraindicated per the EUA label, while deferring to clinical judgement by the investigator as well as consultation with the Sponsor for other listed medications to be used with caution.

The proposed PK sampling schedule for participants not on HD will provide flexibility around the participant's schedule considering the study will be conducted in an outpatient setting and maintains the ability to provide close monitoring for safety. In the HD cohort, the PK schedule takes into consideration the schedule of intermittent HD given three times per week while also maintaining an appropriate dosing schedule to maintain an effective exposure while treating their COVID-19 infection and will inform the effect of HD on the PK of PF-07321332 (nirmatrelvir).

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for PF-07321332 (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 WOCBP (see Appendix 4).

The given study population reproductive capability is limited and the risk of reproductive safety may be minimized because of this. The investigator should determine the participant's potential for becoming pregnant. For women who met Inclusion Criterion 1 in section 5.1 per the investigator's assessment, an acceptable hormone based contraception should be used during the participant's time in the study as described in Section 10.4.4.

4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

Single dose PK study (Study C4671011) of PF-07321332 (nirmatrelvir)/ritonavir in mild, moderate, and severe renal impairment showed that the PF-07321332 (nirmatrelvir) exposure is approximately 3-fold higher and CL/F is 67% lower in severe renal impairment participants relative to healthy volunteers. PF-07321332 (nirmatrelvir) PK data from Phase 2/3 study (Study C4671005) showed PF-07321332 (nirmatrelvir) exposure in mild to moderate COVID-19 patients with Baseline eGFR ≥45 mL/min/1.73 m^2 is comparable to healthy adults. Population PK model-based simulations showed that the PF-07321332

(nirmatrelvir) single dose of 300 mg on Day 1 followed by 150 mg of PF-07321332 (nirmatrelvir) QD on Day 2 to Day 5 with ritonavir 100 mg in severe renal impaired participants gives comparable exposure (AUC_{0-24} and C_{max}) to COVID-19 patients with normal renal function at the 300 mg PF-07321332 (nirmatrelvir)/100 mg ritonavir BID dose for 5 days. Therefore, the PF-07321332 (nirmatrelvir) doses of 300 mg on Day 1 and 150 mg QD on Day 2 to Day 5 were selected for this study.

Ritonavir is mainly eliminated by hepatic metabolism and thus ritonavir PK is not altered in renal impairment participants. Published reports and internal data (C4671011 data on file) show ritonavir PK is comparable between normal healthy participants and severe renal impairment patients and only small fraction of ritonavir dose is removed by HD.[1, 23, 24] Ritonavir 100 mg QD or BID dose has been used for several protease inhibitors (eg, darunavir) with small difference in dose normalized C_{trough} of protease inhibitors. Additionally, the PK of PF-07321332 (nirmatrelvir) with 100 mg QD of ritonavir in severe renal impairment participants is expected to be similar to those of healthy participants taking 100 mg BID of ritonavir. Therefore, the ritonavir dose of 100 mg QD was selected for this study.

The proposed dosing regimen was studied in a non-randomized study in of 15 HD patients with COVID-19 and it was found to be well-tolerated with no SAEs.[20]

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 shown in the SoA for the last participant in the trial globally.

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants ≥18 years of age (or the minimum country specific age of consent if >18) at the time of the Screening Visit.

   - WOCBP may be enrolled.

   - WOCBP must agree to use an effective method of contraception described in Section 5.3. See Appendix 4 for reproductive criteria for male and female participants.

Disease Characteristics:

2. Mild-to-moderate COVID-19 disease as defined in Appendix 9 with confirmed SARS-CoV-2 infection in any specimen collected within 5 days prior to treatment assignment.

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

3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of treatment assignment.

Other Inclusion Criteria:

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

Additional Inclusion Criteria for Cohort 1 (Severe Renally Impaired, and not on HD):

5. Severe renal impairment defined as eGFR <30 mL/min/1.73m^2 (using the 2021 CKD-EPI serum creatinine only eGFR formula in Section 10.7.2.1) measured by clinical laboratory testing on at least 2 occasions, one of which must be within 3 months of Screening and not receiving intermittent HD treatments.

Additional Inclusion Criteria for Cohort 2 (Receiving HD):

6. Receiving stable intermittent HD for at least 6 weeks prior to Screening.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator.

2. Renal transplant recipients.

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

4. Known HIV infection with viral load >400 copies/mL or HIV infection with CD4+ cell count <200/mm^3.

    - Participants in Germany will be excluded if the screening HIV test is positive or if they do not consent to have an HIV test at screening.

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

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

7. 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:

8. Current use of any medications that are highly dependent of CYP3A4 for clearance and which are contraindicated in combination with PF-07321332 (nirmatrelvir)/ritonavir (Appendix 8). Participants taking lovastatin and simvastatin may enroll, provided that they have discontinued use at least 12 hours prior to initiation of PF-07321332 (nirmatrelvir)/ritonavir and refrain from use during treatment and for 5 days after the last dose of PF-07321332 (nirmatrelvir)/ritonavir. Coadministration of PF-07321332 (nirmatrelvir)/ritonavir with medications that are highly dependent on CYP3A4 for clearance may require dose adjustment or additional monitoring (See Appendix 8).

9. Use of any medications or substances that are strong inducers of CYP3A4 and that are contraindicated in combination with PF-07321332 (nirmatrelvir)/ritonavir without the appropriate washout prior to the first dose of PF-07321332 (nirmatrelvir)/ritonavir (see 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.

10. Has received or is expected to receive mAb treatment, convalescent COVID-19 plasma, or anti-viral treatment (eg, molnupiravir, remdesivir) for the current SARS-CoV-2 infection (See Section 6.9).

Prior/Concurrent Clinical Study Experience:

11. Is unwilling to abstain from participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 therapeutics, through the end of study. Previous administration with any investigational 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).

12. Known prior participation in this trial or other trial involving PF-07321332 (nirmatrelvir).

Diagnostic Assessments:

None.

Other Exclusion Criteria:

13. Females who are pregnant or breastfeeding.

14. 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

No contraception methods are required for male participants in this study (see Appendix 4, Section 10.4.1).

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

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

5.3.2. Other Considerations

5.3.2.1. Hemodialysis

Nausea and vomiting are commonly experienced by participants with severe CKD and can be exacerbated during HD treatments. Investigators shall provide guidance to study participants when investigational product dosing and drug absorption may be meaningfully impacted by nausea and/or vomiting. The investigator may refer to the IP manual for further guidance on alleviating nausea and/or vomiting during the treatment period. Examples of measures include but are not limited to taking study intervention with food which may improve tolerability or providing a peppermint following dosing.

Participants on HD (Cohort 2) should take their dose after end of HD on HD days.

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, eligibility details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened as long as they meet eligibility criteria as outlined in Section 5.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and non-investigational 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 PF-07321332 (nirmatrelvir) 300 mg with ritonavir 100 mg on Day 1 and PF-07321332 (nirmatrelvir) 150 mg with ritonavir 100 mg on Days 2 to Day 5.

6.1. Study Intervention(s) Administered

Day 1 of study intervention must be done in the clinic. The participant should receive the study intervention and the site should document that dosing and administration instructions were reviewed with the participant. Patients on HD (Cohort 2) should take their daily dose after HD. See Section 6.2.1.

Intervention Name	PF-07321332 (nirmatrelvir)	Ritonavir
ARM Name (group of patients receiving a specific treatment (or no treatment)	PF-07321332 (nirmatrelvir)/ritonavir	PF-07321332 (nirmatrelvir)/ ritonavir
Type	drug	drug
Dose Formulation	tablet	capsule
Unit Dose Strength(s)	150 mg	100 mg
Dosage Level(s)	300 mg (Day 1), 150 mg (Days 2-5)	100 mg
Route of Administration	oral	oral
Use	experimental	experimental
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IP manual.	Provided centrally by the sponsor. Refer to the IP manual.
Packaging and Labeling	Study intervention will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement and will be open-label.	Study intervention will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement and will be open-label.
Current/Former Name(s) or Alias(es)	PF-07321332/nirmatrelvir	ritonavir

Arm Title	PF-07321332 (nirmatrelvir)/ritonavir (5-Days)
Arm Type	experimental
Arm Description	Participants will receive PF-07321332/ritonavir 300 mg/100 mg on Day 1 followed by PF-07321332/ritonavir 150 mg/100 mg QD from Day 2 to Day 5.
Associated Intervention Labels	PF-07321332 (nirmatrelvir) ritonavir

6.1.1. Administration

Participants in both Cohort 1 and Cohort 2 will be given clear dosing instructions to take a single dose of PF-07321332 (nirmatrelvir)/ritonavir 300 mg/100 mg on Day 1 and PF-07321332 (nirmatrelvir)/ritonavir 150 mg/100 mg QD on Days 2 to 5.

Participants should take the first dose of study intervention on Day 1, during the in-clinic visit; that is, participants should take 2 tablets of PF-07321332 150 mg and 1 capsule of ritonavir 100 mg at the same time. Patients on HD (Cohort 2) should take their daily dose after HD.

On study Day 2, the participant selects a once daily dosing time (Day 2 dose should be taken no earlier than 14 hours and no later than 28 hours after the Day 1 dose). The doses on Days 3-5 should be taken at approximately at the same time (±4 hours) as the Day 2 dose. For participants on HD (Cohort 2), if Day 1 dose is taken on a non-HD day, participants should take the Day 1 dose of study intervention during the in-clinic visit; if Day 1 dose is taken on an HD day, participants should take the Day 1 dose of study intervention in the clinic after HD. On HD days, Cohort 2 participants should take their study intervention after HD.

Participants may take the study intervention with or without food. PF-07321332 (nirmatrelvir) and ritonavir should be taken than approximately 10 minutes or less apart, if feasible, but no more than 15 minutes apart. Refer to the IP manual for additional dosing and administration instructions.

If the participant misses a dose of PF-07321332 (nirmatrelvir)/ritonavir within 12 hours of the time it is usually taken, the participant should take it as soon as possible and resume the normal dosing schedule. If the participant misses a dose by more than 12 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.

6.2. Preparation, Handling, Storage, and Accountability

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 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 re-dispensed to the participants.**

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

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

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using unique container numbers via an IRT system in the cartons provided, in quantities appropriate according to the SoA. A second staff member will verify the dispensing. The participant/caregiver should be instructed to maintain the product in the cartons provided throughout the course of dosing and return the cartons to the site per the SoA.

6.3. Assignment to Study Intervention

The study intervention to be dispensed to the participant will be assigned using an IRT system. The site will utilize the IRT system to assign the DU or container number(s) prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required.

This is an open-label study. The investigator's knowledge of the treatment assignment must not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

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 an open-label study.

6.5. Study Intervention Compliance

Participants will be issued an electronic study intervention diary device or device application (ie, participant or caregiver completed study intervention log) and will be trained how to record the date and time of study intervention dosing on Day 1.

Each day, site personnel will review the electronic dosing diary data during the study intervention period. If any noncompliance with dosing entries is suspected or observed in the data, site personnel will promptly contact the participant to remind them of the relevant study procedures and/or entering the dosing information in the electronic diary as applicable.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the electronic dosing diary. 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.

Study intervention compliance will also be assessed by delegated study personnel upon return of study intervention through counting returned IP and direct questioning, if applicable, review of the electronic study intervention diary and discussion with the participant. Deviation(s) from the prescribed dosage regimen should be recorded in source documents.

A record of the number of PF-07321332 (nirmatrelvir)/ritonavir doses dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

The following noncompliance cases will be considered medication errors (See Section 8.4.10):

- Participants interrupting study intervention for 2 or more consecutive doses;
- Participants taking either PF-07321332 (nirmatrelvir) or ritonavir alone for 2 or more 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. **The Medical Monitor should be notified immediately of any deviation from the prescribed dosing regimen.**

6.6. Dose Modification

Dose modification for PF-07321332 (nirmatrelvir)/ritonavir is not allowed.

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

For this study, any dose of PF-07321332 (nirmatrelvir) greater than 450 mg or ritonavir greater than 200 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

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

6.9. Prior and Concomitant Therapy

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

6.9.1. Permitted During the Study

All participants may receive SoC therapy for COVID-19, in addition to study intervention, unless listed as prohibited medication (see Appendix 8) or as defined in Section 5.2. SoC therapy is defined as any therapy that is approved and used as indicated by the local regulatory authorities (including approvals for emergency use, compassionate use, or through similar regulatory guidance), or any therapy as recommended by a relevant national (or a reputable international) scientific body (eg, WHO, ECDC, CDC, NIH). Sites should consult with the sponsor if a new SoC option becomes available after study initiation. Investigator should ensure that any recommended SoC therapy is not a strong inducer of CYP3A4 or highly dependent on CYP3A4 for clearance.

For participants taking phosphate binders, a minimum of 2 hours between administration of study drug and phosphate binders should be applied.

6.9.2. Prohibited in the study

Participants must not receive convalescent COVID-19 plasma treatment for COVID-19, antiviral treatment (eg, molnupiravir, remdesivir), or mAb for the treatment of COVID-19, during the study period.

PF-07321332 (nirmatrelvir)/ritonavir are inhibitors of CYP3A4. Therefore, medications highly dependent on CYP3A4 for clearance and which are contraindicated in combination with PF-07321332 (nirmatrelvir)/ritonavir (see Appendix 8) are prohibited during study intervention (from Day 1 and prior to the first dose of study intervention, if clinically appropriate).

Participants taking lovastatin and simvastatin should discontinue use at least 12 hours prior to initiation of PF-07321332 (nirmatrelvir)/ritonavir and refrain from use during treatment and for 5 days after the last dose of PF-07321332 (nirmatrelvir)/ritonavir.

Coadministration of PF-07321332 (nirmatrelvir)/ritonavir with medications that are highly dependent on CYP3A4 for clearance may require dose adjustment or additional monitoring. Investigators should reference Appendix 8 for a list of these medications and consult the Pfizer medical monitor for guidance on coadministration with PF-07321332 (nirmatrelvir)/ritonavir.

Medications or substances that are highly dependent on CYP3A4 for clearance or are strong inducers of CYP3A4 and that are contraindicated in combination with PF-07321332 (nirmatrelvir)/ritonavir must be discontinued for an appropriate washout period prior to the first dose of PF-07321332 (nirmatrelvir)/ritonavir and are prohibited for the duration of the study intervention period and for 4 days after the last dose of PF-07321332 (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; a minimum washout period of 28 days prior to dosing of study intervention is required.

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 (including 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 the study intervention;
- Requirement for prohibited concomitant medication;
- Death;
- Pregnancy;
- Study terminated by sponsor;
- Withdrawal by participant or legally authorized representative;

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for 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 a participant is hospitalized, study intervention may continue to be administered, as feasible, and based on medical judgement of the investigator.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

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

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

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

7.3. Lost to Follow-Up

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

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

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

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing

address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

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

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

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

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

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

Procedures conducted as part of the participant's routine clinical management (eg, eGFR) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

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

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

The total blood sampling volume for individual participants in this study is approximately 120 mL for Cohort 1 and approximately 150 mL for Cohort 2 over approximately 36 days. 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.

8.1.1. Tasso sample training and collection

Participants (and/or caregivers) completing Tasso M20 device training will use the Tasso M20 device at home to collect PK samples during the times specified in the PK schema. Samples collected at the site that are not specified to be arterial port or venous port samples for HD participants (Cohort 2) will also be simultaneously collected by site staff using the Tasso device and venous sample blood draw. At Screening (or during the Screening Period) participants and/or caregivers will be instructed on administration of the Tasso M20 device and will demonstrate their understanding by self-collecting or a caregiver collecting a sample on site using this device. This sample is for training purposes and no testing will be performed on it. Participants unwilling or unable to complete Tasso training and applied demonstration of the tool, may utilize support from a caregiver to administer the Tasso device. If the site finds the participant (or caregiver) is willing and able to correctly administer the device, the participant will enter the study and go home with sufficient quantities of the Tasso device as well as all required study materials per protocol. The site will document participant's and/or caregiver's training in source and confirm the participant has continued the required Tasso sample collection on Day 2 at home via a telehealth visit. Additional site support and training may be required for participants.

If a participant (or caregiver) is unwilling or cannot demonstrate proficiency collecting the sample using the Tasso device, then the site must document the participant as a screen failure based on the inclusion criteria in Section 5 unless the participant has the option to use a home healthcare provider as described in Section 8.1.4.

8.1.2. Medical History

Medical history in addition to COVID-19 disease history and demographics will be collected at screening. Smoking status will be collected. Complete medication history of all prescription or nonprescription drugs (including vaccinations), adjunctive therapeutic procedures (non-drug treatments and procedures), and dietary and herbal supplements taken within 30 days prior to the planned first dose will be collected. All doses of COVID-19 vaccinations administered at any time before study participation will be collected.

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. See Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record any new adjunctive therapeutic procedures (non-drug treatments and procedures) or changes in adjunctive therapeutic procedures 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. See Appendix 4.
- Review and record any COVID-19 related hospitalizations and emergency department visits which have occurred since the last visit.
- Study participants must be reminded to promptly notify site staff about any change in their health status.
- Any other activities listed as per the SoA.

8.1.4. Home Health Visits

A home health care service 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 any new adjunctive therapeutic procedures (non-drug treatments and procedures) or changes in adjunctive therapeutic procedures since the last contact.
- Review and record any COVID-19 related hospitalizations and emergency department visits which have occurred since the last visit.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Collect clinical laboratory, PK, and biomarker samples in accordance with the SoA.

CCI [redacted]

- Perform a targeted PE per the SoA.
- Collect Vital Signs per the SoA.
- Any other activities per the SoA

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. COVID-19-Related Medical Visit Details

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

COVID-19-related hospitalization is defined as admission to inpatient care for the treatment of clinical manifestations of COVID-19 of any duration. Participants who are waiting in an emergency department or other hospital unit for an inpatient bed to become available are considered hospitalized provided that a decision to admit to inpatient care has occurred. The definition of hospitalizations also 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.

8.3. Safety Assessments

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

8.3.1. Targeted Physical Examinations

A targeted physical examination will include, at a minimum, general appearance, abdominal exam including assessment of ascites, distension, and organomegaly, lungs and cardiovascular systems.

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

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

8.3.2. Height and Weight

Height and weight will be measured and recorded as source data at screening. Height may be self-reported.

On HD treatment days, record the pre- and post- dialysis weight on the appropriate CRF. Refer to CRF completion guidelines.

8.3.3. Vital Signs

Temperature, PR, respiratory rate, and oxygen saturation rate will be assessed in all participants as specified in the SoA. Temperature should be measured using the same method for all study visits.

Blood pressure and PR measurements will be assessed in a supine or seated position with their feet on the floor when possible with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and PR measurements should be preceded by at least 5 minutes of rest in a semi-supine or sitting position for the participant in a quiet setting without distractions (eg, television, cell phones).

On HD treatment days record the last available BP measurement in the appropriate CRF. Refer to the CRF completion guidelines.

Vital signs are to be taken before blood collection for laboratory tests.

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.

8.3.4. Clinical Safety Laboratory Assessments

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

Laboratory safety parameters will be graded according to DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.[22] 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.

8.3.5. Pregnancy Testing

Local urine testing using the central lab-provided test (locally purchased test is acceptable after Day 1 if the participant and/or home health staff does not have one provided by the central lab) will be standard for the protocol unless serum testing is required by local regulation or IRB/EC or the participant is anuric. Pregnancy tests (β-hCG) must have a sensitivity of at least 25 mIU/mL. A negative urine or serum (β-hCG) pregnancy test must be confirmed at screening or Day 1 prior to treatment for ALL women of childbearing potential (WOCBP). Following a negative pregnancy test result at screening, appropriate contraception must be commenced. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations.

8.3.5.1. At-Home Pregnancy Testing

If a participant requiring pregnancy testing cannot visit a local laboratory or have a central lab-provided pregnancy test, 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 home pregnancy test kit will be provided by the central lab. The pregnancy test outcome should be documented in the participant’s source documents/medical records and relevant data recorded on the CRF. If the pregnancy test is positive, the EDP should be reported (Section 8.4.5.1). 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/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 or participant's partner, the investigator must report this information to Pfizer Safety using the PSSA and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 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 and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed PSSA is maintained in the investigator site file.

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

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. **Lack of efficacy or failure of expected pharmacological action in an approved indication constitutes an SAE and should be reported to Pfizer Safety**.

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.

- See Section 6.5 for potential errors related to study intervention compliance not listed above.

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 the PSSA **only when associated with an SAE.**

8.5. Pharmacokinetics

8.5.1. Non-Hemodialysis

Participants assigned to Cohort 1 will begin study intervention on Day 1 and the PK samples collected will follow the PK Sampling Schema in Section 1.3.

8.5.2. Hemodialysis

Participants assigned to Cohort 2 will begin study intervention either on a HD treatment day or non-HD treatment day. The day of the participant's first IP dose, either on an HD day or on a non-HD day (ie, Treatment Day 1) will determine the subsequent PK sample schedule as described in the PK Sampling Schema.

Participants beginning IP administration on an HD treatment day (ie, Treatment Day 1) will have PK samples collected per the PK Sampling schema in Section 1.3 including samples drawn from HD lines before and during HD treatment days. Obtain blood samples for **hematology (hematocrit)** at time 0 (venous port sample) and time of the last PK draw (venous port sample) on dialysis, to be used for dialysis clearance (CLd) calculations. Time 0 is defined as the time period prior to the start of the HD blood pump.

If the participant is assigned to begin IP treatment (ie, Treatment Day 1) on a non-HD day, the participant will have samples collected per the PK Sampling Schema in Section 1.3. Obtain blood samples for hematology (hematocrit) at time 0 (venous port sample) and time of the last PK draw (venous port sample) on dialysis, to be used for dialysis clearance (CLd) calculations. Time 0 is defined as the time period prior to the start of the HD blood pump.

Additional details regarding the HD treatment will be captured in the database (refer to CRF completion guidelines).

8.5.3. PK Samples for Analysis of PF-07321332 (nirmatrelvir) and Ritonavir

PK samples for measurement of PF-07321332 (nirmatrelvir) and ritonavir plasma concentrations will be collected, using Tasso M20 device for dried blood. If Tasso device is not available or unable to function properly, then a venous blood sample must be drawn. For plasma samples, a blood sample of approximately 4 mL, to provide approximately 1.5 mL plasma, will be collected for measurement of plasma concentrations of PF-07321332 (nirmatrelvir) and ritonavir as specified in the SoA. For Tasso sampling, approximately 100 µL of blood is collected. Instructions for the collection, handling, and recording of biological samples will be provided in the laboratory manual or by the sponsor. The date and time (12-hour clock time) of collection for each sample will be recorded on the sample requistion forms that are submitted to the laboratories.

The ritonavir concentration will be measured using Tasso samples collected and/or venous blood sample collected and will be reported as plasma concentration listings only (no PK analysis of ritonavir data).

If a participant cannot attend a clinic visit, PK samples may be collected via home health visit, self-collected or caregiver-collected using the Tasso M20 device to collect whole blood microsamples to measure PF-07321332 (nirmatrelvir) and ritonavir concentrations.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples per the PK sampling times in Section 1.3 relative to dosing.

Both Tasso sample and venous blood samples will be used to evaluate the PK of PF-07321332 (nirmatrelvir) and ritonavir. Samples collected for analyses of PF-07321332 (nirmatrelvir) and ritonavir concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method [redacted].

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

Samples collected for measurement of plasma concentrations of PF-07321332 (nirmatrelvir) and ritonavir will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with [redacted] validated [redacted] methods.

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

8.5.4. Blood to Plasma Ratio Analysis of PF-07321332 (nirmatrelvir) and Ritonavir

As specified in the SoA, exploratory PK venous blood samples of approximately 4 mL each for the measurement of PF-07321332 (nirmatrelvir) and ritonavir concentrations will be collected to evaluate microsampling PK approach using the Tasso® M20 device. These venous blood samples will be collected at 2 time points immediately either before or after Tasso sample collection but no more than 15 minutes apart between the Tasso and venous blood samples. Venous blood samples of approximately 4 mL will be collected, a portion of it will be aliquotted for blood and the remaining blood will be centrifuged to harvest plasma in K2EDTA for nirmatrelvir and ritonavir blood/plasma ratio measurements.

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

Samples collected for measurement of plasma concentrations of PF-07321332 (nirmatrelvir) and ritonavir will be analyzed using a validated analytical method in compliance with applicable SOPs.

8.5.5. Electronic diary (eDiary)

All participants will be provided an electronic handheld device (eDiary) or will download the eDiary application on their own device to record times of study intervention administration. **All dosing times must be entered into the eDiary by the participant (or caregiver) within 24 hours of taking the dose of study intervention.**

Participants will receive daily reminders to complete eDiary entries on their own (or by caregiver) as specified on the SoA. The eDiary should be completed at approximately the same time every day.

Compliance will be monitored daily during treatment by the site staff and by the sponsor. If a participant experiences any issues with the Tasso M20 device, electronic diary entry, or study intervention, they should contact the site immediately for appropriate mitigating actions.

Noted issues with compliance will be escalated to the sponsor as per the agreed upon electronic diary review plan.

8.6. Genetics

8.6.1. Specified Genetics (Not Applicable)

Specified genetics are not included 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 laboratory manual.

8.7. Biomarkers

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

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

CCI [redacted]

- A 6 mL blood sample optimized for plasma may be utilized for proteomics and immunologic studies.

8.7.1. Viral Load Assessments

CCI [redacted]

CCI [redacted] Residual SARS-CoV-2 RNA concentration samples may be utilized for viral sequencing to assess for signs of viral evolution and evaluation of potential genetic viral variants (eg, 3CL gene) SARS CoV-2 infectivity assays, and additional molecular analysis.

Residuals of all samples may be stored and used for additional analyses related to COVID-19 and/or the mechanism of action of PF-07321332 (nirmatrelvir)/ritonavir. Storage and shipping instructions will be in accordance with the laboratory manual.

8.7.2. Specified Protein Research

8.7.2.1. Specified Biomarker Research (Plasma)

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 studies and/or analysis of SARS-CoV-2 by RT-PCR. Residuals of all samples may be stored and used for additional analyses related to COVID-19 and/or the mechanism of action of PF-07321332 (nirmatrelvir)/ritonavir. Storage and shipping instructions will be in accordance with the laboratory manual.

8.7.3. 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

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.

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

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Medical resource utilization will be evaluated in this study (see Section 8.2.1).

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

As this is a single-arm study, there will be no treatment comparisons, and all analyses will be descriptive.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"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 assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
SAS	All participants assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

Defined Analysis Set	Description
PK Concentration	The PK concentration population is defined as all participants assigned to investigational product and treated who have at least 1 concentration measured.
PK Parameter	The PK parameter analysis population is defined as all participants assigned to investigational product and treated who have at least 1 of the PK parameters of interest measured.

9.3. Statistical Analyses

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

9.3.1. General Considerations

Descriptive statistics for all endpoints by each cohort and visit will be provided.

The number of participants screened, intervention assigned in treatment phase, completing the study drug administration, and completing the study will be summarized.

The reason for all discontinuations will be summarized by each cohort.

Baseline demographic and other characteristics will be tabulated for the SAS and summarized by each cohort. Quantitative variables will be described by standard descriptive statistics (mean, standard deviation, minimum, and maximum), and qualitative variables will be summarized by frequency tables with number and proportion in each category (with the corresponding sample sizes).

For continuous endpoints, change from baseline over time will be summarized for each cohort and overall.

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

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

9.3.2. Primary Endpoints Analyses

TEAEs will be summarized with the number and percent of participants in the SAS through Day 34 for two cohorts and overall.

The incidence of SAEs and AEs leading to discontinuation will be summarized in the SAS through Day 34 for two cohorts and overall.

9.3.3. Secondary Endpoints Analyses

PF-07321332 (nirmatrelvir) plasma concentration data will be analyzed using a population PK analysis approach (nonlinear mixed effects models). Pharmacokinetic parameters including CL/F, C_{max}, C_{min}, $AUC_{0\text{-}tau}$ will be provided for PF-07321332 (nirmatrelvir) based on the final population PK model. A stand-alone population PK modeling and simulation analysis plan will be prepared and the results will be reported in a stand-alone report, outside the clinical study report.

PK parameters including $AUC_{0\text{-}tau}$, C_{max}, C_{trough}, CL/F and Vz/F will be estimated from the population PK model by each cohort. HD clearance (CLd) and fraction of dose (Fd) of PF-07321332 (nirmatrelvir) removed from the body by dialysis will be calculated for Cohort 2 (participants on HD).

Individual PF-07321332 (nirmatrelvir) plasma concentration profiles, using the PK analysis set for Cohorts 1 to 2, will be presented graphically using actual sample collection time on both linear and semilogarithmic scales, showing all participants on a single plot for each cohort. Median concentration time profiles will be presented on both linear and semilogarithmic scales using nominal sampling time. Additional graphical presentations of PK data may be included at the discretion of the PK scientist.

In addition, the PF-07321332 (nirmatrelvir) plasma concentrations, participant demographics, and disease status data will be combined with data from appropriate previous clinical studies in adult participants for a population PK analysis. The actual dosing and plasma sampling times will be used for the analysis. A stand-alone population PK modeling and simulation analysis plan will be prepared and the results will be reported in a stand-alone report, outside the clinical study report. Pharmacokinetic parameters including CL/F, C_{max}, C_{min}, $AUC_{0\text{-}tau}$ will be provided for PF-07321332 (nirmatrelvir) based on the final population PK model.

A listing of PF-07321332 (nirmatrelvir) plasma concentrations at the nominal sampling time by participant and cohort will be provided. For each Cohort 1 and 2, the plasma concentration will be summarized by nominal sampling time using appropriate descriptive statistics (eg, number of participants/samples, mean, SD, minimum, median, maximum, geometric mean, and coefficient of variation).

For summary statistics by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used. Box and whisker plots for individual participant parameters (AUC_{inf} and C_{max}) will be constructed by each cohort and overlaid with geometric means.

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9.3.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

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

Medical history and physical examination collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4. Interim Analyses

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

9.5. Sample Size Determination

The sample size of 12 evaluable participants per cohort is considered to provide a suitable estimate of precision of PK parameters of PF-07321332 (nirmatrelvir) in severe renal impairment participants on HD and not on HD, as this provided 40% precision (the width of

90% confidence interval) for AUC_{inf} and C_{max}. To ensure sufficient PK data for analysis, any participant with insufficient PK samples for analysis may be replaced.

To identify an adequate sample size for the PK, we assessed the precision of estimating the PK parameter using different sample sizes, as defined by the width of the resultant confidence intervals represented as a percentage of the mean value of the PK parameter. Currently, no PK data is available in severe renal impairment following multiple doses of PF-07321332 (nirmatrelvir); therefore, we used single dose PK data of PF-07321332 (nirmatrelvir) in severe renal impairment adults not on dialysis (Table 1) to determine the CV estimates for PF-07321332 (nirmatrelvir) PK parameters. As illustrated in Table 1, the CV estimates for PF-07321332 (nirmatrelvir) AUC_{inf} and C_{max} range from 33% to 38% (ie, 0.33 to 0.38).

Table 1. PF-07321332 (nirmatrelvir) PK Parameters Following Single Dose of PF-07321332 (nirmatrelvir)/Ritonavir 100 mg/100 mg in Severe Renal Impairment Patients

PK Parameter (units)	PF-07321332 (nirmatrelvir) (N=8)
C_{max} (ng/mL)	2369 (38)
AUC_{inf} (ng*hr/mL)	44040 (33)
T_{max} (hr)	3.00 (1.00-6.05)
$t_{1/2}$ (hr)	13.37 ± 3.3225

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $t_{½}$.

Since we anticipate that study participants may experience more variability in PK parameters than the available data given the wider range of multiple doses, precision is described with an anticipated CV of 0.2, 0.3, or 0.4.

Table 2 below shows the upper and lower confidence limits and 90% CI width for the mean PK parameter (eg, AUC, $t_{½}$, or C_{max}), presented as a percentage of the mean, for different N and CV. With a sample size of 12 evaluable patients and a CV equal to 0.4, the 90% CI will range from 79.3% – 120.7 % of the mean, and the corresponding CI width will be 41.4% of the mean. This rather tight CI would indicate whether or not the study findings reveal a higher than 40% difference from the PK parameter in a severe renal impaired population.

Table 2. Percentile Range and Width of 90% Confidence Intervals for the Mean PK Parameter

N	CV=0.2		CV=0.3		CV=0.4	
	Range	Width	Range	Width	Range	Width
8	86.6-113.4%	26.8%	79.9-120.1%	40.2%	73.2-126.8%	53.6%
10	88.5-111.5%	23.1%	82.7-117.3%	34.6%	76.9-123.1%	46.2%
12	89.6-110.4%	20.7%	84.5-115.5%	31.1%	**79.3-120.7%**	**41.4%**
14	90.5-109.5%	19.0%	85.8-114.2%	28.4%	81.1 -119.0%	37.9%

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 sub-investigators 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

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).

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use the program-level E-DMC which is independent of the study team and includes only external members, and is responsible for the ongoing monitoring of the

efficacy and safety of participants in the program's studies according to the E-DMC charter. This study is not assessing efficacy and assessing only safety. The E-DMC charter describes the role of the E-DMC in more detail for this study. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision as appropriate. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events of safety data, as well as those that are not endpoints, to regulatory authorities and investigators, as appropriate.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

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

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

10.1.8. Source Documents

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

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

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

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

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

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

10.1.9. Study and Site Start and Closure

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

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.
- Sites may be closed early if the enrollment is completed earlier than anticipated in one country but ongoing in other countries.

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 3. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Other	Additional Tests
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and creatinine CystatinC and eGFR Glucose Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein	Pregnancy test (β-hCG)[a] SARS-CoV-2 serology (IgG and IgM) HIV Testing [b]	**For suspected DICI/DIKI:** Creatinine (Scr) CystatinC (Scys) eGFR (Scr only and combined Scr+Scys) Spot (dipstick) UACR **Needed for Hy's Law** AST, ALT (repeat) Total bilirubin (repeat) Albumin Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels Hepatitis serology

a. Local urine testing using the central lab-provided test (locally purchased test is acceptable after Day 1 if the participant and/or home health staff does not have one provided by the central lab) will be standard for the protocol unless serum testing is required by local regulation or IRB/EC or the participant is anuric. A negative urine or serum (β-hCG) pregnancy test must be confirmed at screening and prior to dispensing treatment for ALL WOCBP.
b. 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.

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 Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs 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 and EDP Supplemental Form; 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 Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, 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.

- 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. • If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT will be taken 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

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

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

  OR

- Is a WOCBP and agrees to use an acceptable contraceptive method: intrauterine device (IUD), dual barrier method, partner vasectomy, or abstinence, 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). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

Because ritonavir may reduce the effect of estradiol-containing contraceptives when agents are co-administered, a barrier method or other nonhormonal method of contraception must also be used if the participant is using estradiol-containing contraceptives during the 5 days of PF-07321332 (nirmatrelvir)/ritonavir treatment and until one menstrual cycle after stopping study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective non-estrogen 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.
        - A negative urine pregnancy test must be confirmed at screening or Day 1 prior to dispensing treatment for all women unless they are 50 years or older with no menses for 12 months.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

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

Sexual Abstinence

6. 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 (not highly effective) may be used concomitantly with option 6 above 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).

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 PF-07321332 (nirmatrelvir)/ritonavir or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

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

- The samples will be retained as indicated:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

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

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

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

10.7.2. Age-Specific Kidney Function Calculation Recommendations

Sites will use the provided calculator to calculate eGFR: https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr

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

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

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10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

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

PF-07321332 (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 PF-07321332 (nirmatrelvir)/ritonavir without the appropriate washout prior to the first dose of PF-07321332 (nirmatrelvir)/ritonavir are prohibited. 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; a minimum washout period of 28 days prior to dosing of study intervention is required. PF-07321332 (nirmatrelvir)/ritonavir are inhibitors of CYP3A4. Therefore, medications highly dependent on CYP3A4 for clearance and which are contraindicated in combination with PF-07321332 (nirmatrelvir)/ritonavir are prohibited during study intervention (from Day 1 and prior to the first dose of study intervention to Day 5, if clinically appropriate).

Participants taking lovastatin and simvastatin should discontinue use at least 12 hours prior to initiation of PF-07321332 (nirmatrelvir)/ritonavir and refrain from use during treatment and for 5 days after the last dose of PF-07321332 (nirmatrelvir)/ritonavir.

Medications or substances that are highly dependent on CYP3A4 for clearance or are strong inducers of CYP3A4 and that are contraindicated in combination with PF-07321332 (nirmatrelvir)/ritonavir must be discontinued for an appropriate washout period prior to the first dose of PF-07321332 (nirmatrelvir)/ritonavir and are prohibited for the duration of the study intervention period and for 4 days after the last dose of PF-07321332 (nirmatrelvir)/ritonavir.

A non-exhaustive list of prohibited and precautionary medications is provided below in Table 4. **If a medication is not listed as contraindicated, it should not automatically be assumed it is safe to co-administer.** Appropriately qualified site staff will review all concomitant medications to determine if they are prohibited. Investigators should consult the ritonavir product label and the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use and consult with the Sponsor medical monitor as appropriate to maintain participant safety.

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 judgement 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 study intervention, availability of new information in literature on the DDI potential of other drugs).

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

Table 4. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension.
Analgesics	pethidine, propoxyphene	↑ pethidine ↑ propoxyphene	Co-administration contraindicated due to potential for serious respiratory depression or hematologic abnormalities.
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 arrhythmia.
Antiarrhythmics	bepridil, lidocaine (systemic)	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ PF-07321332 (nirmatrelvir)/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance.
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 rivaroxaban	↑↓ warfarin ↑ rivaroxaban	Closely monitor INR if co-administration with warfarin is necessary. Increased bleeding risk with rivaroxaban. Avoid concomitant use.

Table 4. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	dabigatran	↑ dabigatran	Increased bleeding risk with Dabigatran. Avoid concomitant use with dabigatran.
Anticonvulsants	carbamazepine, phenobarbital, phenytoin	↓PF-07321332 (nirmatrelvir)/ritonavir ↑ carbamazepine ↓ phenobarbital ↓ phenytoin	Co-administration contraindicated due to potential loss of virologic response and possible resistance.
Antidepressants	bupropion trazodone	↓ bupropion and active metabolite hydroxy-bupropion ↑ trazodone	Monitor for an adequate clinical response to bupropion. 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, ketoconazole, isavuconazonium sulfate itraconazole	↓ voriconazole ↑ketoconazole ↑isavuconazonium sulfate ↑itraconazole ↑PF-07321332 (nirmatrelvir)/ritonavir	Avoid concomitant use of voriconazole. Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
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.

Table 4. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anti-HIV protease inhibitors	amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir	↑protease Inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PF-07321332 (nirmatrelvir)/ritonavir or protease inhibitor adverse events with concomitant use of these protease inhibitors.
Anti-HIV	didanosine, delavirdine, efavirenz, maraviroc, nevirapine, raltegravir, zidovudine bictegravir/ emtricitabine/ tenofovir	↑ didanosine ↑ efavirenz ↑ maraviroc ↓ raltegravir ↓ 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.
Antimycobacterial	rifampin	↓ PF-07321332 (nirmatrelvir)/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered.
Antimycobacterial	bedaquiline rifabutin	↑ bedaquiline ↑ rifabutin	Refer to the bedaquiline product label for further information. Refer to rifabutin product label for further information on rifabutin dose reduction.
Antipsychotics	lurasidone, pimozide, clozapine	↑ lurasidone ↑ pimozide ↑ clozapine	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias.

Table 4. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
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.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PF-07321332 (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 PF-07321332 (nirmatrelvir)/ritonavir with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.
Endothelin receptor Antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PF-07321332 (nirmatrelvir)/ritonavir. Refer to the bosentan product label for further information.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.

Table 4. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Hepatitis C direct acting antivirals	elbasvir/grazoprevir, glecaprevir/pibrentasvir	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. It is not recommended to co-administer ritonavir with glecaprevir/pibrentasvir.
	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 PF-07321332 (nirmatrelvir)/ritonavir or HCV drug adverse events with concomitant use.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ PF-07321332 (nirmatrelvir)/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
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 PF-07321332 (nirmatrelvir)/ritonavir and refrain from use during treatment and for 5 days after the last dose of PF-07321332 (nirmatrelvir)/ritonavir.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with

Table 4. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			PF-07321332 (nirmatrelvir)/ritonavir..
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PF-07321332 (nirmatrelvir)/ritonavir treatment and until one menstrual cycle after stopping PF-07321332 (nirmatrelvir)/ritonavir.
Immunosuppressants	cyclosporine, tacrolimus, sirolimus	↑ cyclosporine ↑ tacrolimus ↑ sirolimus	Therapeutic concentration monitoring is recommended for immunosuppressants. Avoid use of PF-07321332 (nirmatrelvir)/ritonavir when close monitoring of immunosuppressant serum concentrations is not feasible. Avoid concomitant use of sirolimus and PF-07321332 (nirmatrelvir)/ritonavir. If co-administered, refer to individual product label for immunosuppressant for further information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Co-administration is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Narcotic analgesics	fentanyl methadone	↑ fentanyl ↓ methadone	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with PF-07321332 (nirmatrelvir)/ritonavir. Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.

Table 4. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
PDE5 inhibitor	sildenafil (Revatio®) when used for pulmonary arterial hypertension	↑ sildenafil	Co-administration contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope.
Sedative/hypnotics	triazolam, oral midazolam	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression.
Sedative/hypnotics	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.
Systemic corticosteroids	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, prednisone, triamcinolone	↑ corticosteroid	Increased risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone should be considered.

10.9. Appendix 9: Country-Specific Requirements

10.9.1. Germany

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

10.10. Appendix 10: Definition of COVID-19 Severity

The severity of a COVID-19 infection for this study is classified using the below criteria developed by NIH (Clinical Spectrum | COVID-19 Treatment Guidelines [nih.gov]):

- Asymptomatic or Presymptomatic Infection:
  - Individuals who test positive for SARS-CoV-2 using a virologic test (ie, a NAAT or an antigen test) but who have no symptoms that are consistent with COVID-19.
- Mild Illness:
  - Individuals who have any of the various signs and symptoms of COVID-19 (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
- Moderate Illness:
  - Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO^2) ≥94% on room air at sea level.
- Severe Illness:
  - Individuals who have SpO^2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO^2/FiO^2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.
- Critical Illness:
  - Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

10.11. Appendix 11: Protocol Amendment History

Amendment 1 (23 Jun 2022)

Overall Rationale for the Amendment: To update from BID to QD dosing schedule; clearly delineate PK sample collection schemas for Cohort 1 and for Cohort 2 when HD is given on specific days; clarify that the Tasso device is the preferred method of PK sampling; and clarify eDiary data collection and other study procedures.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
1. Protocol Summary 4. Study Design 6. Study Intervention(s) and Concomitant Therapy	Nirmatrelvir/ritonavir 100 mg /100 mg Q12 hr dose on Days 1-5 changed to a single dose on Day 1 of PF-07321332 (nirmatrelvir)/ritonavir 300 mg/100 mg followed by PF-07321332 (nirmatrelvir)/ritonavir 150 mg/100 mg QD on Days 2-5.	Considering the uncertainty in safety in this vulnerable population, higher exposure with BID dosing regimen is concerning. Population PK model-based simulations showed that 300 mg PF-07321332 (nirmatrelvir) on Day 1 and 150 mg of PF-07321332 (nirmatrelvir) QD on Day 2 to Day 5 with 100 mg ritonavir gives comparable exposure to COVID-19 patients with normal renal function at the 300 mg PF-07321332 (nirmatrelvir)/100 mg ritonavir BID dose for 5 days.	Substantial (impacts scientific value/ conduct/management of the trial).
1.2 Schema	Revised for QD dosing.	Revised for QD dosing.	Substantial (impacts scientific value/ conduct/management of the trial.
1.3 SoA 6. Study Intervention(s) and Concomitant Therapy	Revised dosing windows to allow for Day 1-Day 2 to be no earlier than 14 hours and no later than 28 hours after the Day 1	Revised for QD dosing.	Substantial (impacts scientific value/ conduct/management of the trial.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	dose and for the remaining doses (Days 3-5) to be taken at approximately the same time (±4 hours) as the Day 2 dose.		
1.3 PK Sampling Schemas	Additional PK sampling tables were added for Cohort 2.	Tables were added to for both cohorts to show the different PK collection scenarios as related to dosing and HD.	Substantial (impacts scientific value/ conduct/management of the trial).
8.4. AEs, SAEs, and Other Safety Reporting 10.3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting	Revised CT SAE Report Form to PSSA.	This study will use the PSSA tool for reporting SAEs.	Nonsubstantial
1. Inclusion Criteria 5. Study Population 10.4.1 Male Participant Reproductive Inclusion Criteria	Inclusion criterion 1 revised: deletion of requirement for male contraception.	Exposure to females through seminal fluid will be sufficiently low and therefore precludes the need for male contraception.	Nonsubstantial
1.1. Synopsis 5. Study population	Exclusion criterion 3 revised.	Simplification of chronic liver disease criteria. This update includes removal of need for INR testing at screening.	Nonsubstantial
1.1. Synopsis 5. Study population	Exclusion criterion 4 revised.	HIV medications are not prohibited but will be reviewed during concomitant medication review per	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
		Screening procedures and Appendix 8.	
6.5. Study Intervention Compliance	Updated definitions of medication errors.	Revised for QD dosing.	Nonsubstantial
1.3. Schedule of Activities	Added maximum time between dosing of the two study interventions as 15 minutes.	To allow additional time between taking the study interventions.	Nonsubstantial
1.3 SoA 8.1.1. Tasso Sample Training and Collection	Tasso device instruction.	Clarification that use of Tasso device is the preferred method of PK sampling. If Tasso device is not available or unable to function properly, only then is a venous draw permitted.	Nonsubstantial
8.1.4. Home Health Visits	Addition of the procedure to review and record COVID-19 related hospitalizations.	Correction of an important end point omission.	Nonsubstantial
1.3 SoA 8.5.4 Electronic diary	Clarification of eDiary use and addition of investigative site compliance check.	Clarification of eDiary use and requirement of compliance check by the investigative site.	Nonsubstantial
CCI [redacted]			
9.5. Sample Size Determination	Added that participants may be prelaced.	To ensure sufficient PK data for analysis, any participant with insufficient PK samples for analysis may be replaced.	Nonsubstantial
1. Protocol Title, Rationale, Inclusion Criteria	Minor word changes, administrative.	Clarification.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
8.7 Biomarkers Table 4, Appendix 10			
Throughout the protocol	Electronic diary will not be used to collect PK sample times.	PK collection times will be captured on the sample requisition forms that are submitted to the laboratories.	Nonsubstantial
Throughout the protocol	Changed "nirmatrelvir" to "PF-07321332 (nirmatrelvir)".	To be consistent with study drug bottle labeling.	Nonsubstantial

10.12. Appendix 12: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}tau}$	AUC over a dosing interval
AUC_{inf}	AUC from time 0 extrapolated to infinite time
AxMP	auxiliary medicinal product
BID	twice daily
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology
CL/F	apparent oral clearance
CLd	hemodialysis clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
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
C_{trough}	Pre-dose trough concentration
CV	coefficient of variation
CYP	cytochrome P450
DAIDS	Division of AIDS
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury

Abbreviation	Term
DILI	drug-induced liver injury
DU	dispensable unit
EC	ethics committee
EC90	90% effective concentration
ECC	emergency contact card
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
eDiary	electronic diary
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
ET	early termination
EU	European Union
EUA	Emergence Use Authorization
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
Fd	fraction of drug removed from the body
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HA	health authority
HCP	healthcare provider
HCV	hepatitis C virus
HD	hemodialysis
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
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
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual

Abbreviation	Term
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IV	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LFT	liver function test
mAb	monoclonal antibody
M^{pro}	main protease
MQI	medically qualified individual
N	number of
NA	not applicable
NAAT	nucleic acid amplification test
NHP	non-human primates
NIH	National Institutes of Health
NIMP	non-investigational medicinal product
NOAEL	no adverse event observed level
NP	nasopharyngeal
PaO^2/FiO^2	ratio of arterial partial pressure of oxygen to fraction of inspired oxygen
PDE5	phosphodiesterase type 5
PE	physical examination
PK	pharmacokinetic(s)
PopCL	population clearance
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QD	daily
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
SAS	safety analysis set
Scr	serum creatinine
Scys	serum cystatin C
SD	standard deviation
SoA	schedule of activities
SoC	standard of care
SOP	standard operating procedure
SpO^2	oxygen saturation
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction

Abbreviation	Term
T bili	total bilirubin
$t_{½}$	terminal half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
T_{max}	maximum plasma concentration
UACR	urine albumin/creatinine ratio
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
Vz/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
β-hCG	β-human chorionic gonadotropin

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