A PHASE 2/3, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF 2 REGIMENS OF ORALLY ADMINISTERED PF-07321332/RITONAVIR IN PREVENTING SYMPTOMATIC SARS-COV-2 INFECTION IN ADULT HOUSEHOLD CONTACTS OF AN INDIVIDUAL WITH SYMPTOMATIC COVID-19

Study Intervention Number:	PF-07321332
Study Intervention Name:	NA
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ClinicalTrials.gov ID:	NCT05047601
Protocol Number:	C4671006
Phase:	2/3

Brief Title: A Phase 2/3 Postexposure Prophylaxis Study of PF-07321332/Ritonavir in Adult Household Contacts of an Individual With Symptomatic COVID-19

Document History

Document	Version Date
Amendment 2	25 January 2022
Amendment 1	20 August 2021
Original protocol	02 July 2021

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

Amendment 2 (25-January-2022)

Overall Rationale for the Amendment:

Considering the high anti-SARS-CoV-2 antibody seropositivity rate observed in Study C4671006 participants recruited to date, the lower-than-expected event rate (symptomatic SARS-CoV-2 infection confirmed by RT-PCR), efficacy data from Study C4671005, and emerging data on the Omicron variant of the SARS-CoV-2 virus, this amendment includes updates to the definition for the primary endpoint events, the timing of the interim analysis and associated statistical considerations, assumptions for sample size estimation, and a provision to permit enrollment of previously vaccinated participants.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 3. OBJECTIVES, ENDPOINTS, and ESTIMANDS Section 9.1. Section 9.1.1. Estimands Section 9.1.1.2 Section 9.1.2. Multiplicity Adjustment Section 9.3.1. General Considerations	Primary objective, endpoint, and estimand updated to include rapid antigen test-confirmed SARS-CoV-2 infection. Updated the secondary objective and secondary endpoint to assess viral titers in participants with a positive RT-PCR result at baseline.	Updated to reduce the possibility of missing a laboratory confirmed SARS-CoV-2 infection (and therefore a potential primary endpoint event) possibly related to participant swab collection methodology.

Section # and Name	Description of Change	Brief Rationale
Section 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis Section 9.3.3. Key Secondary Efficacy Endpoint(s)/Estimand(s) Analysis Section 9.3.4. Secondary Endpoint(s)/Estimand(s) Analysis		
Section 1.1. Synopsis Section 4.1. Overall Design Section 9.4. Interim Analyses Section 10.1.5.1. Data Monitoring Committee	• Updated the timing of the planned interim analysis from 45% to 70% of enrollment (ie, when approximately 70% of overall participants have completed the Day 14 assessments with the minimum number of 24 symptomatic infection events). • Updated the O'Brien-Fleming boundary accordingly based on the timing of the planned interim analysis.	To maximize the amount of data for the Omicron variant in the interim dataset.
Section 1.1. Synopsis Section 4.1. Overall Design Section 9.5. Sample Size Determination	Increased the sample size to reflect the adjustment of the relative risk reduction and the placebo event rate.	Updated based on results in Study C4671005 and the relative risk reduction and the incidence of primary endpoints events observed in the REGEN-COV postexposure prophylaxis study and baseline seropositivity rate observed in the study.
Section 1.3. Schedule of Activities Section 6.2.1. Preparation and Dispensing	Added text to specify when study intervention is to be dispensed.	For clarification.

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Assessments Section 8.2.5. Electrocardiograms Section 10.7. Appendix 7: ECG Findings of Potential Clinical Concern	Section removed as ECGs are no longer required per Dear Investigator Letter dated 31 August 2021.	Updated to reflect changes from the Dear Investigator Letter.
Section 1.3. Schedule of Activities Section 8.2.1. Medical History	Added note regarding prior documented infection and details of vaccination.	• For clarification.
Section 1.3. Schedule of Activities Section 8.6.4.2	• Specified that nasal swabs will be collected by the HCP on Days 5, 10, and 14, or during any COVID-19 Signs and Symptoms Onset visit or unplanned visit. Also specified for in-person visits that occur on the same day as self collection of the nasal swab that the HCP should collect the nasal swab. • Nasal swab collection was to be done under observation by site staff during specified in-person visits as per PACL dated 14 December 2021.	• To ensure accurate collection of nasal swab data. • Updated to reflect changes from PACL.
Section 2.2. Background	• Updated the number of COVID-19 cases and deaths worldwide. • Added text about SARS-CoV-2 variants of concern in relation to vaccine efficacy.	• To provide recent data. • To provide background on emerging variants of concern with respect to vaccine efficacy and risk for reinfection.
Section 2.2.2. Clinical Overview	Added results from Study C4671005 and the 45% interim analysis results from Study C4671002.	To provide a brief summary of available clinical efficacy and safety data.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.2. Benefit Assessment	• Described 2 orally administered antivirals that have received EUA in the US and EU. • Updated benefit assessment.	• To describe treatment options for COVID-19 in patients at high risk of progression to severe COVID-19. • To support the potential benefit of treatment and postexposure prophylaxis.
Section 5.2. Exclusion Criteria	• Updated Exclusion Criteria #1 to exclude participants with a prior documented infection within 6 months of the screening visit. Also updated Exclusion Criterion # 14 to exclude participants who received any SARS-CoV-2 vaccine within 6 months prior to screening or were expected to receive a SARS-CoV-2 vaccine, or other approved, authorized, or investigational postexposure prophylaxis treatment through Day 38. • For Exclusion Criterion #13, specified that participants who have received approved, authorized, or investigational anti-SARS-CoV-2 mAb, convalescent plasma, other drugs for treatment of COVID-19, or other anti-SARS-CoV-2 biologic products within 6 months of screening would be excluded. • Added clarification to Exclusion Criterion #7 to align with the exclusion criterion in Appendix 11.	• Updated Exclusion Criterion #1 because emerging data related to the omicron variant suggest a higher risk for reinfection with SARS-COV-2 and that protection afforded by current vaccines against symptomatic infection due to the omicron variant wanes after several months. Exclusion Criterion #14 has been updated to allow participants who have been previously vaccinated to be enrolled because they may benefit from postexposure prophylaxis. • To facilitate inclusion of previously infected participants who may have been treated with a product that could confound efficacy assessments. • Updated Exclusion Criterion #7 to reflect changes from the PACL dated 13 October 2021.
Section 6.1.1. Administration	Co-administration of PF-07321332 and ritonavir should be at the same time, but no more than 10 minutes apart is acceptable.	Added language to specify what is considered to be an acceptable time for co-administration of PF-07321332 and ritonavir.

Section # and Name	Description of Change	Brief Rationale
Section 6.3.2. Blinding of the Sponsor	Language was added to provide additional information about the study unblinding plan.	To provide additional information so that an unblinded submission team could be formed at the time of an interim analysis for preparing unblinded analyses and documents to support regulatory activities.
Section 6.8. Concomitant Therapy	For medications permitted during the study, clarified that any authorized or approved COVID-19 therapy would result in study intervention discontinuation. Added antiviral treatment for COVID-19 to the prohibited medications during the study.	Based on the availability of EUA oral antiviral and mAb treatments.
Section 9.3.1 General Considerations	Summarized possible combinations of RT-PCR and rapid antigen test results that may be available for a participant and how these results would be considered toward confirming SARS-CoV-2 infection in the analyses of the primary and relevant secondary endpoints.	Based on the updates to the primary and relevant secondary endpoints where, in addition to RT-PCR, rapid antigen test results may also confirm SARS-CoV-2 infection.
Section 9.2. Analysis Sets	Removed reference to postbaseline measurement in the analysis set definitions.	Updated based on FDA feedback.
Appendix 12. Country Specific Requirements	Removed France country-specific guidance.	Was previously included in error.
Appendix 12: Section 10.12.3. Bulgaria	Added Bulgaria country-specific guidance regarding Exclusion Criteria #3 and #5.	To incorporate country-specific changes into the global protocol and to align with the 26 October 2021 PACL.
Appendix 12: Section 10.12.4. Ukraine	Added Ukraine country-specific guidance regarding nasal swab collection.	To incorporate country-specific changes into the global protocol and to align with the 22 December 2021 PACL.
Section 10.8. Appendix 8: Prohibited Concomitant Medications That May Result in DDI	• Updated table. • Corrections and updates to the list of precautionary and	• To align with the Emergency Use Authorization Fact Sheet for Paxlovid™.[1]

Section # and Name	Description of Change	Brief Rationale
	prohibited medications as per PACL dated 29 September 2021.	• Updated to reflect changes from the PACL.
Section 10.9. Appendix 9. Signs and Symptoms Consistent with COVID-19	Added fatigue (low energy or tiredness) to targeted symptoms for analysis.	Was inadvertently omitted in the previous version.
10.13 Appendix 13. Protocol Amendment History	Modified with Amendment 1 changes.	Per Pfizer protocol template.
Throughout	Other administrative edits.	Updated to provide clarity.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2/3, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study To Evaluate The Safety And Efficacy Of 2 Regimens Of Orally Administered PF-07321332/Ritonavir In Preventing Symptomatic SARS-CoV-2 Infection In Adult Household Contacts Of An Individual With Symptomatic COVID-19.

Brief Title: A Phase 2/3 Postexposure Prophylaxis Study of PF-07321332/Ritonavir in Adult Household Contacts of an Individual with Symptomatic COVID-19

Rationale

The purpose of this study is to evaluate the efficacy and safety of PF-07321332/ritonavir as postexposure prophylaxis for adult household contacts of an individual with symptomatic COVID-19.

Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing symptomatic RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14.	• The risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline and are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.
Secondary:	**Secondary:**	**Secondary:**
• To describe the safety and tolerability of 5-day and 10-day regimens of PF-07321332/ritonavir relative to placebo in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	• Incidence of TEAEs • Incidence of SAEs and AEs leading to discontinuation.	• Not applicable.
• To compare the efficacy of 5-day and 10-day regimens of	Of the participants who have a negative RT-PCR result at baseline and who are	• The risk reduction between 5-day and 10-day regimens of

Objectives	Endpoints	Estimands
PF-07321332/ritonavir versus placebo in preventing symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection in adult participants who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19.	at increased risk of severe COVID-19 illness: • Proportion of participants with symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. • Proportion of participants with COVID-19 related hospitalization or death from any cause by Day 28.	PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing SARS-CoV-2 infection in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with asymptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. • Time to RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. Of the participants who have a positive RT-PCR result at baseline: • Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. Of the participants who have a negative or positive RT-PCR result at baseline: • Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14.	• Not applicable.
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the duration and severity of COVID-19 related signs and symptoms in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with no, mild, moderate, or severe signs and symptoms attributed to COVID-19 through Day 28. • Number of days of symptomatic SARS-CoV-2 infection through Day 28.	• Not applicable.
• To determine the PK of PF-07321332 in adult participants who have a negative	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable.

Objectives	Endpoints	Estimands
or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.		
• To describe all-cause mortality in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with death (all-cause) through Day 38.	• Not applicable.
• To describe the viral load in nasal samples over time in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Viral titers measured via RT-PCR in nasal swabs over time. Of the participants who have a positive RT-PCR result at baseline: • Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.
• To describe hospitalizations in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Number of days of hospital and ICU stay in participants with COVID-19-related hospitalization through Day 28.	• Not applicable.
• To describe COVID-19 related medical visits in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Number of COVID-19 related medical visits through Day 28.	• Not applicable.

Overall Design

Brief Summary

This Phase 2/3, randomized, double-blind, double-dummy, placebo-controlled study in approximately 2880 participants who have a negative screening SARS-CoV-2 rapid antigen test result and who are asymptomatic household contacts of individuals who are symptomatic and recently tested positive for SARS-CoV-2 (index case: defined as patient with symptomatic COVID-19) will compare the efficacy of 2 regimens of PF-07321332/ritonavir versus placebo. Index cases may be participants in Phase 2/3 safety and efficacy studies of PF-07321332/ritonavir (C4671002 and C4671005), but this is not required. Eligible participants for this study will be randomly assigned (1:1:1) within 96 hours after collection of the index case's first positive SARS-CoV-2 test to treatment in 1 of 3 intervention groups.

Randomization will be stratified based on the presence of risk factors associated with severe COVID-19 illness and geographic region at screening.

Number of Participants

Assuming approximately 5% of participants will have a positive RT-PCR result at baseline, and assuming an approximately 10% dropout rate, the total sample size for this study will be approximately 2880 participants.

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

Intervention Groups and Duration

Eligible participants for this study (C4671006) will be randomly assigned (1:1:1) within 96 hours after collection of the index case's first positive SARS-CoV-2 test to receive:

- PF-07321332/ritonavir q12h for 5 days followed by matching placebo q12h for 5 days; or
- PF-07321332/ritonavir q12h for 10 days; or
- Matching placebo for PF-07321332/ritonavir q12h for 10 days.

Participants will be screened within 24 hours before randomization. The total duration of the study is up to 42 days and includes screening, study intervention through Day 10, efficacy assessments through Day 14, and a safety follow-up period through Day 38 [±3 days].

Data Monitoring Committee or Other Independent Oversight Committee: Yes

An independent E-DMC will review unblinded data to ensure the safety of participants on an ongoing basis throughout the duration of the study. In addition to up to weekly reviews of safety data, the E-DMC will review the following:

- Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 150 participants have completed Day 10 of the study, at which point enrollment will be paused pending E-DMC review of the safety data. After review of the sentinel cohort, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.
- Interim analysis: An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by the E-DMC after a prespecified accrual of participants (ie, before or at approximately 70% overall participants have completed

the Day 14 assessments with a minimum number of 24 participants having symptomatic infection [mITT analysis set]).

Statistical Methods

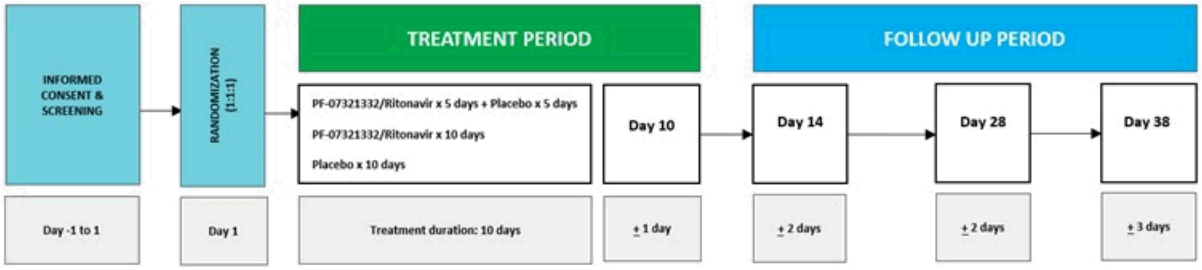
For the primary efficacy analysis, GEE will be used to analyze the proportion of participants with a negative RT-PCR result at baseline who develop a symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for each treatment group. Comparisons between 5-day regimen of PF-07321332/ritonavir versus placebo group and 10-day regimen of PF-07321332/ritonavir versus placebo group will be presented as risk reduction with 95% CIs based on GEE analysis.

Based on the results from Study C4671005, which showed PF-07321332/ritonavir treatment significantly reduced the risk of hospitalization or death from any cause by 89% compared with placebo in nonhospitalized symptomatic adult participants with COVID-19 who were at increased risk of progression to severe disease when they were treated within 3 days of symptom onset, and the high relative risk reduction (approximately 80%) observed in Regeneron REGEN-COV post-exposure prophylaxis study, the risk reduction between PF-07321332/ritonavir group versus placebo group is assumed to be 70%. The symptomatic infection rate assumption in the placebo group is adjusted to 4% based on the observed seropositivity rate in this study and the impact of seropositivity on the incidence of primary endpoint events in the REGEN-COV post-exposure prophylaxis study where the incidence of symptomatic infection was 2% in participants who were seropositive and 8% in those who were seronegative.[2]

Among baseline RT-PCR negative participants, assuming an 4% symptomatic infection rate in the placebo group, a 70% reduction in symptomatic infection (1.2% symptomatic infection rate) in the PF-07321332/ritonavir group (5-day and 10-day regimen), a sample size of 821 participants per group (2463 participants total) will provide approximately 90% power for each comparison between 5-day and 10-day regimens of PF-07321332/ritonavir group versus placebo group under a 2-sided type-1 error rate of 5%. Assuming approximately 5% of participants with negative rapid antigen test at screening will have a positive RT-PCR result at baseline, and assuming an approximately 10% dropout rate, the total sample size for this study will be approximately 2880 participants.

An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by an independent E-DMC after a prespecified accrual of participants (ie, before or at approximately 70% overall participants have completed the Day 14 assessments with a minimum number of 24 participants having symptomatic infection [mITT analysis set]).

1.2. Schema


INFORMED CONSENT & SCREENING
RANDOMIZATION (1:1:1)
TREATMENT PERIOD
FOLLOW UP PERIOD
PF-07321332/Ritonavir x 5 days + Placebo x 5 days
PF-07321332/Ritonavir x 10 days
Placebo x 10 days
Day 10
Day 14
Day 28
Day 38
Day -1 to 1
Day 1
Treatment duration: 10 days
± 1 day
± 2 days
± 2 days
± 3 days

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 Abbreviations used in this table may be found in Appendix 14.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 28**	**Day 38 EOS**	**COVID-19 Signs/ Symptoms Onset**	**ET**	**NOTES**
Visit Window	**Day -1 to Day 1**	**0 days**	**± 1 day**	**± 1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**+2 days**		
ELIGIBILITY											
Informed consent	X										See Section 10.1.3.
Verify inclusion/exclusion criteria	X										See Section 5.1 and Section 5.2.
Demographics & medical history	X										Will include assessment of prior documented infection and details of vaccination. See Section 8.2.1.
COVID-19 risk factor assessment	X										See Appendix 11.
Index Case Characteristics	X										• As permitted by local laws and regulations, index case characteristics will be collected through interview with the study participant to aid in characterization of the exposure period. • See Section 8.1.5

Visit Identifier Abbreviations used in this table may be found in Appendix 14.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 28**	**Day 38 EOS**	**COVID-19 Signs/ Symptoms Onset**	**ET**	**NOTES**
Visit Window	**Day -1 to Day 1**	**0 days**	**± 1 day**	**± 1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**+2 days**		
PHYSICAL EXAM AND VITAL SIGNS											
Targeted physical examination	X	X		X	X	X		X	X	[X]	• Will be completed at all in-person visits. In the event that an in-person visit is not feasible at the investigational site, targeted physical examinations and vital signs assessment may be performed by a licensed HCP at an alternate site approved by the investigator (eg, the participant's home) when feasible.
Vital signs	X	X		X	X	X		X	X	[X]	• AEs should be assessed by means of a telemedicine visit if not feasible during an in person visit. • Previously identified AEs (either by interview, physical exam, or other assessment) should be monitored to the extent possible if telemedicine is used. • Vital signs assessment at the COVID-19 Signs/Symptoms Onset visit will include oxygen saturation. • See Section 8.2.4.
Weight, height	X										See Section 8.2.2.
CLINICAL LABORATORY TESTS											
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. If deemed necessary, laboratory assessments at screening will be performed at the local laboratory. The medical laboratory

Visit Identifier Abbreviations used in this table may be found in Appendix 14.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 28**	**Day 38 EOS**	**COVID-19 Signs/ Symptoms Onset**	**ET**	**NOTES**
Visit Window	**Day -1 to Day 1**	**0 days**	**± 1 day**	**± 1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**+2 days**		
Blood chemistry		X		X	X	X*		X*		[X]	test abnormalities within 6 months prior to screening must be closely assessed. If abnormalities cannot be verified, consider conducting local laboratory testing at screening to confirm eligibility for the study. • Baseline laboratory assessments should be collected prior to first dose of study intervention. If post-screening eGFR is <45 mL/min/1.73m^2, the participant will be instructed to discontinue any remaining study intervention doses as soon as study staff become aware of the eGFR results. If another baseline laboratory result meets protocol Section 5.2 exclusionary values and the participant is still receiving study treatment, contact the Medical Monitor. • If a baseline laboratory result meets Section 5.2 exclusionary laboratory values and the participant is still receiving study treatment, the investigator should contact the Medical Monitor. • Abnormal laboratory values related to AEs should be followed until resolution. See Section 8.2.5 and Appendix 2. • *Safety laboratory tests at Days 14 and 38 are required only if clinically significant abnormal laboratory values were present from a sample drawn at the previous study visit
Other laboratory assessments		X		X	X	X		X		[X]	

Visit Identifier Abbreviations used in this table may be found in Appendix 14.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 28**	**Day 38 EOS**	**COVID-19 Signs/ Symptoms Onset**	**ET**	**NOTES**
Visit Window	**Day -1 to Day 1**	**0 days**	**± 1 day**	**± 1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**+2 days**		
											when laboratory assessments were performed. • At Day 14 and Day 38, serology is collected for all participants.
Pregnancy test	X							X		[X]	• A negative urine or serum (β-hCG) pregnancy test must be confirmed at Screening for WOCBP only. • 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 38 or ET. • See Section 8.2.6 and Appendix 2.
FSH	X										• FSH is to be performed locally in female participants <60 years of age at Screening who are not using hormonal contraception or hormonal replacement therapy, to confirm postmenopausal status. Female participants aged 50 to 60 years with no menses for 12 months do not need FSH confirmation. • When FSH testing is required to confirm postmenopausal status, a participant may be enrolled in the study prior to the test result being available as long as the FSH test result confirms postmenopausal status prior to dosing. • See Section 10.4.3 and Appendix 2.

Visit Identifier Abbreviations used in this table may be found in Appendix 14.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 28**	**Day 38 EOS**	**COVID-19 Signs/ Symptoms Onset**	**ET**	**NOTES**
Visit Window	**Day -1 to Day 1**	**0 days**	**± 1 day**	**± 1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**+2 days**		
Rapid antigen test	X								X		See Section 8.6.4.1. Collected as a separate swab from nasal swab, specifically for local testing.
Nasal swab		Daily from Day 1 through Day 14							X	X	• At baseline, a nasal swab will be self collected by the participant to determine RT-PCR status (+ or -); this test will not be used to determine study eligibility. The baseline sample will be collected under observation by site staff to ensure correct collection method. Thereafter, nasal swabs will be self collected by the participant at about the same time each day, preferably in the morning, except on Day 5, Day 10, Day 14, or during any COVID-19 Signs and Symptoms Onset visit or unplanned visit, in which case, the nasal swab should be collected by the HCP. • On the days where there is an in-person visit, the nasal swab should be collected by the HCP and the participants instructed to not collect the nasal swab before the visit • See Section 8.6.4.2. and Section 8.6.5.
Specified protein research (plasma biomarkers)		X		X		X					See Section 8.6.2.
[redacted] CCI											

Visit Identifier Abbreviations used in this table may be found in Appendix 14.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 28**	**Day 38 EOS**	**COVID-19 Signs/ Symptoms Onset**	**ET**	**NOTES**
Visit Window	**Day -1 to Day 1**	**0 days**	**± 1 day**	**± 1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**+2 days**		
											CCI
Retained research samples for biomarkers (Prep B2)		X		X		X		X			• See Section 8.6.5.
PHARMACOKINETICS											
PK Sample (PF-07321332)		X		X							• On Day 1, one blood sample for PK will be collected 30 to 90 minutes postdose for those participants who receive their first dose onsite and are able to remain onsite following dose administration. • On Day 5, one blood sample for PK will be collected predose (up to 2 hours before study intervention administration) if feasible; otherwise, collect anytime during the visit. • See Section 8.4.

Optional PK samples (self collected by participant)			X								• Whole blood self-collected PK samples using the Tasso microsampling device (selected sites, if feasible) at the following times:
											  • Day 3: after the morning dose at the following times:
											  ○ 1 sample between 30 to 90 minutes,
											  ○ 1 sample between 2 to 6 hours, and
											  ○ 1 sample 8 to 12 hours after the dose (the last sample should be collected before the evening dose).

Visit Identifier Abbreviations used in this table may be found in Appendix 14.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 28**	**Day 38 EOS**	**COVID-19 Signs/ Symptoms Onset**	**ET**	**NOTES**
Visit Window	**Day -1 to Day 1**	**0 days**	**± 1 day**	**± 1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**+2 days**		
											• See Section 8.4.
RANDOMIZATION		X									
STUDY INTERVENTION											
Study intervention dispensation		X		X							• Study intervention will be dispensed on Day 1 and Day 5 (see Section 6.1.1). • Day 5 visit has to be scheduled on time to dispense study intervention prior to the 11th dose which should be on the morning of study Day 6 if 2 doses were taken on Day 1 or on the evening of study Day 6, if a single dose was taken on Day 1.
Study intervention administration		Daily from Day 1 through Day 10									• **For Treatment Days**: Participants will receive 20 doses of study intervention over 10 days. The first dose will be administered on Day 1. The second dose will be administered at least 4 hours later so that the dosing schedule is convenient for the participant. All subsequent doses will be q12h [±30 minutes]. • The last day of treatment will be Day 11 if only 1 dose was administered on Day 1.
STUDY PROCEDURES AND ASSESSMENTS											
Collect/update secondary contacts		X		X	X	X	X	X			On Day 1, the investigator will collect contact information for at least 2 individuals who can be contacted if the participant cannot be reached after multiple attempts (repeat/update as needed).
Record/update household characteristics		X		X	X	X	X	X	X	X	See Section 8.1.6.

Visit Identifier Abbreviations used in this table may be found in Appendix 14.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 28**	**Day 38 EOS**	**COVID-19 Signs/ Symptoms Onset**	**ET**	**NOTES**
Visit Window	**Day -1 to Day 1**	**0 days**	**± 1 day**	**± 1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**+2 days**		
Record supplemental oxygen requirements		X		X	X	X	X	X	X	X	See Section 8.1.4.
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 study diary (COVID-19 signs and symptoms and global impression questions)		Daily from Day 1 through Day 28									• Global impression questions will be answered every day from the first day a symptom is reported in the diary through Day 28. • These assessments will be answered on the day of the COVID-19 Signs/ Symptoms Onset visit or the ET visit if the visit occurs from Day 1 through Day 28. • For participants who are using an eDiary provided through the study, the eDiary will be collected on Day 38 or ET visit, after completion of all logs and questionnaires executed on the device. See Section 8.1.1 and Section 8.1.7.3.
EQ-5D-5L		X		X	X	X		X			• If supported by technology, PRO assessments will be reported by participants in the study diary (Section 8.1.1). • See Section 8.1.7.
WPAI				X		X		X			
Staff review of study diary		X		X	X	X	X	X	X	X	
Participant completes study intervention log		Daily from Day 1 through Day 10									• The last day of treatment will be Day 10 or Day 11, depending on how many doses were administered on Day 1. • Study intervention log will be completed on the day of the

Visit Identifier Abbreviations used in this table may be found in Appendix 14.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 28**	**Day 38 EOS**	**COVID-19 Signs/ Symptoms Onset**	**ET**	**NOTES**
Visit Window	**Day -1 to Day 1**	**0 days**	**± 1 day**	**± 1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**+2 days**		
											COVID-19 Signs/ Symptoms Onset or ET visits if the visit occurs from Day 1 through Day 10.
Record COVID-19 related medical visits since last visit					X	X	X	X	X	X	• **Day 10**: Record visits since randomization. • **All subsequent visits**: Record COVID-19 related medical visits since the prior assessment/visit. • See Section 8.1.3
Retrieval of unused study intervention and empty study intervention containers				X	X	X		X		[X]	• Empty study intervention containers and unused study intervention should be returned at the next in-person visit. • See Section 6.4.
Study intervention accountability					X	X				[X] if needed	
Contraception check	X	X		X	X	X	X	X	X	X	See Appendix 4.
Vital status								X		X	
Record prior/concomitant medication(s)	X	X		X	X	X	X	X	X	X	• All prescription and over-the-counter medications being taken by the participant and any vaccine for 14 days before study entry (considered prior treatment) will be recorded. • Refer to Section 6.8.
Record adjunctive therapeutic procedures	X	X		X	X	X	X	X	X	X	• Nondrug treatments. • Collected only if the participant becomes symptomatic.
SERIOUS AND NONSERIOUS AE MONITORING	X	X		X	X	X	X	X	X	X	• AEs should be assessed by means of a telemedicine visit if not feasible via an in-person visit. • Refer to Section 8.3.

- Site staff should, in discussion with participants, determine the most appropriate location to conduct study visits, whether in-person or remotely by telemedicine. In person visits should take place at the investigational site. If investigational site in-person visit is not feasible, then alternate venues may include the participant's home or an alternate, noninvestigational site location approved by the investigator. If an in-person visit is held at a location other than the investigational site, in certain situations the assigned HCP

Visit Identifier Abbreviations used in this table may be found in Appendix 14.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 28**	**Day 38 EOS**	**COVID-19 Signs/ Symptoms Onset**	**ET**	**NOTES**
Visit Window	**Day -1 to Day 1**	**0 days**	**± 1 day**	**± 1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**+2 days**		

performing the visit may be unable to complete all assessments. In these cases, a telemedicine visit should also occur to perform the remaining assessments. Remote visits can be conducted using a telemedicine system approved for use at the site.

- Assessments indicated in brackets [X] will be performed only for in-person visits.
- **Screening** procedures may be done from Day -1 to Day 1. In many cases, all screening procedures can be completed in <24 hours. For these participants, screening procedures may be completed on the same calendar day as randomization and Baseline/Day 1 procedures, including first dose of study intervention.
- **Baseline** assessments should be performed before the administration of the first dose of study intervention.
- **Day 1** is the start of dosing.
- **Study Intervention Dispensation:** Participants will receive their first set of study intervention containers at the Day 1 visit and the second set of study intervention containers at the Day 5 visit. Each set contains 10 doses of study intervention. Day 5 visit should be scheduled so that there is no interruption in dosing and so the participant does not use any overage from the set dispensed at the Day 1 visit (see Section 6.2.1).
- **For Study Intervention Administration**: Participants will receive study intervention for 10 days (20 doses total). The first dose will be administered at the Baseline/Day 1 visit during the in-person visit, if possible. All subsequent doses (ie, 19) will be self administered outside the study clinic (eg, at home).
- **Screening**, **Baseline**, **Day 5, Day 10, Day 14 and Day 38** visits will be conducted in person (at the investigational site or another location, including a participant's home) provided the planned assessments can be performed at the location selected.
- **Day 3** visit involves self-collected PK samples (using Tasso) only for participants who consent to the optional PK sampling. There is no planned in-person or telemedicine visit on this study day.
- **Day 3** and **Day 5** visits should be conducted on separate calendar days.
- **Day 28** visit will be conducted by telemedicine system.
- **COVID-19 Signs/Symptoms Onset** visit will occur as soon as possible after the participant experiences signs or symptoms of COVID-19 and will be conducted in-person any time up to Day 38. When the COVID-19 Signs/Symptoms Onset visit occurs within the visit window prior to a scheduled visit, the 2 visits can be combined.
- **Early Termination** visit will be conducted in person or by telemedicine system.
- **Telemedicine Visits**, while planned to be virtual (ie, over the phone or other approved system), they may also be conducted in-person at the investigator's discretion.

2. INTRODUCTION

PF-07321332, a potent and selective SARS-CoV-2 3CL protease inhibitor, is being investigated as oral antiviral postexposure prophylaxis for adult household contacts of an individual with symptomatic COVID-19.

2.1. Study Rationale

The purpose of this study is to evaluate the efficacy and safety of PF-07321332/ritonavir as postexposure prophylaxis for adult household contacts of an individual with symptomatic COVID-19.

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[3] on 30 January 2020 and further characterized the disease outbreak as a pandemic on 11 March 2020.[4] As of 12 January 2022, at least, 315 million cases have been confirmed worldwide, and at least 5.5 million deaths have occurred.[5]

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,[6] patients who are hospitalized with COVID-19 may have significant morbidity and mortality, [7,8] 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,[6] patients who are hospitalized with COVID-19 may have significant morbidity and mortality,[7,8] 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.[9-12] Moreover, other comorbidities, such as hypertension, obesity, and diabetes, as well as older age and male sex increase the risk for worse outcomes.[7]

Although there are symptomatic and/or supportive treatments for COVID-19, few antiviral drugs are available or in late-stage development to help treat COVID-19 in patients with mild to moderate COVID-19. Existing compounds, such as hydroxychloroquine and lopinavir/ritonavir, have been evaluated as potential treatment options for COVID-19, but have not demonstrated benefit or efficacy beyond the SoC.[13-15] The FDA has approved IV remdesivir,[16] an antiviral drug with activity against SARS-CoV-2, for hospitalized patients with COVID-19. However, remdesivir monotherapy may not be sufficient in all subsets of patients[17] across the COVID-19 spectrum or has shown modest effects.[18,19] Favipiravir is currently under investigation for its activity against SARS-CoV-2 due to its broad-spectrum activity against various RNA viruses[20,21] and has been approved in India and Russia to treat mild to moderate COVID-19.[22] Although favipiravir has been generally well tolerated in clinical studies primarily for the treatment of the influenza virus, teratogenic findings in multiple animal species at exposures comparable to those achieved with the dosage regimen to treat influenza have limited its clinical use.[20]

Among contacts of persons with COVID-19, the percentage in whom new cases develop (secondary attack rate) has been estimated at 10 to 15%.[23-26] The primary infection-control strategy currently employed relies on basic hygiene measures such as hand washing, use of personal protective equipment such face masks, social distancing, and isolation of case patients and their contacts.[27] The effectiveness of isolation depends on the promptness of the intervention, the level of contact tracing, and the level of isolation adherence[28]. Implementation of these measures however, has not been fully effective and spread of SARS-CoV-2 in many countries continues to occur. Furthermore, modeling of SARS-CoV-2 viral shedding dynamics suggests that up to 44% of transmission occurs prior to symptom onset of the index case (presymptomatic transmission) and that start and peak infectiousness can be up to 2 days before symptom onset.[29]

There are large efforts in progress to develop vaccines[30] with several now authorized for emergency use or conditionally approved by Health Authorities for those aged 12 years and older.[31] These vaccines will take time to deploy and may not be taken by everyone. Also, the duration of potential protection is not known leading to continued efforts to identify effective antiviral treatments. Moreover, currently authorized/approved vaccines may not be as effective against potential outbreaks from new coronavirus variants.[32,33] Emergence of the Omicron variant in late 2021 provides an example of the potential impact emerging variants of SARS-CoV-2 may have on vaccine efficacy. More specifically, gene mutations in the Omicron variant appear to result in vaccine efficacy against symptomatic disease that is significantly lower than against the Delta variant.[34] Regarding protection afforded by prior infection with SARS-CoV-2, the Omicron variant appears to be associated with a 3- to 8-fold increased risk of reinfection relative to other variants that have been observed.[35]

Postexposure prophylaxis for healthy contacts is among the measures used for outbreak control of several infectious diseases (eg, pandemic influenza).[36] No oral agents are known to be effective in preventing SARS-CoV-2 infection or COVID-19, but aminoquinolines (hydroxychloroquine and chloroquine) and antiretrovirals (eg, lopinavir/ritonavir) have been or are in the process of being assessed for potential utility in the postexposure, preemptive treatment/prophylaxis outpatient settings.[37] The direct reduction of viral replication, through inhibition of other critical viral enzymes, offers an important mechanism to achieve greater patient benefit and perhaps aid in control of the COVID-19 pandemic. The US FDA has granted EUA for an IV- or SC-administered mAb regimen as postexposure prophylaxis for COVID-19 in adults and adolescents who are at high risk for progressing to severe COVID-19.[38] As of January 2022, no orally administered therapeutic intervention has been approved or authorized for use in postexposure/preemptive treatment/prophylaxis.

The coronavirus 3CL protease is a virally encoded enzyme that is critical to the SARS-CoV-2 replication cycle, analogous to other obligatory virally encoded proteases (eg, HIV Protease, HCV Protease).[39] Mutagenesis experiments with other coronaviruses and picornaviruses that are related to SARS-CoV-2 (picornavirus-like supercluster) have demonstrated that the activity of the 3CL protease (or the corresponding picornaviral 3C enzyme) is essential for viral replication. No close human analogs of coronavirus 3CL

enzymes are known, suggesting that appropriate 3CL inhibitors may function as selective inhibitors of SARS-CoV-2 and other coronaviruses as therapeutic agents.

PF-07321332, a potent and selective inhibitor of the SARS-CoV-2 3CL protease, is being developed as an oral treatment and/or postexposure prophylaxis in patients with COVID-19.

In this study, PF-07321332 will be coadministered with ritonavir. Ritonavir is a strong CYP3A4 inhibitor and is being used as a PK enhancer in this study to inhibit the metabolism of PF-07321332 in order to increase plasma concentrations of PF-07321332 to values that are anticipated to be efficacious. Ritonavir, at the dose administered in this study, is not expected to have any antiviral activity on the SARS-CoV-2 virus and is being used only as a PK enhancing agent .

2.2.1. Nonclinical Studies of PF-07321332

Data from nonclinical studies support the planned clinical trials with PF-07321332; these studies are described in the IB.[40]

PF-07321332 exhibits a broad-spectrum activity across the Coronaviridae family of 3CL proteases demonstrating its potential for antiviral efficacy.

In vitro, PF-07321332 inhibited SARS-CoV-2 viral-induced cytopathic effect in monkey kidney Vero cell assays. PF-07321332 exhibited antiviral activity against SARS-CoV-2 in dNHBE cells. Furthermore, PF-07321332 inhibited HCoV229E viral-induced cytopathic effect in human MRC-5 cells with no detectable cytotoxicity at the highest compound concentration tested.

Test article-related findings identified in the safety pharmacology studies included changes in locomotor activity and transient higher respiratory rate and minute volume in rats at the high dose, as well as minor and transient hemodynamic changes (increased blood pressure and decreased heart rate) at the high dose in cynomolgus monkeys. The potential effects on safety pharmacology parameters are monitorable in the clinic, and no correlated clinical signs or histopathological findings in the relevant organs were observed in the 14-day or 15-day repeat dose GLP toxicity studies in rats or monkeys. ECG data were also collected in the 15-day GLP monkey study and there were no test article-related changes in ECG parameters (HR, RR-, PR-, QRS-, QT-, QTc-intervals) or ECG morphology in that study.

2.2.2. Clinical Overview

C4671001 (NCT04756531) is an ongoing FIH single and multiple dose escalation study to evaluate the safety, tolerability, and PK of PF-07321332 in healthy adult participants. Preliminary data from this study collected as of 07 April 2021 (SAD) and 14 April 2021 (MAD) in a total of 31 participants who were randomized and treated with PF-07321332 or placebo, the clinical safety profile of PF 07321332 appears to be acceptable at single doses up to 1500 mg alone and up to 750 mg administered with ritonavir (100 mg at -12h, 0h, 12h), and at repeated daily doses administered orally for 10 days of up to 500 mg PF-07321332 BID with 100 mg ritonavir BID.

Preliminary PK data on Day 1, Day 5 and Day 10 following multiple oral administration of PF-07321332/ritonavir 75/100 mg, 250/100 mg, and 500/100 mg BID suggest less than proportional increase in exposures at steady state. Multiple dosing over 10 days achieved steady state on Day 2 with approximately 2-fold accumulation. Day 5 and Day 10 exposure was similar at all doses.

Following single doses of PF-07321332 with and without ritonavir, all AEs were mild and none were considered treatment related. There were no obvious trends in, or association of, TEAEs with dose level of PF-07321332. Following multiple doses, the most commonly observed AEs by SOC were Gastrointestinal disorders and Nervous system disorders. Diarrhea was the most common reported AE, occurring in 4 participants across treatment groups. A total of 5 treatment related TEAEs were observed in Part-2:MAD.

Across treatment groups, blood TSH increased in 3 participants, and 2 participants reported dysgeusia. The 3 participants with elevated TSH results did not experience related clinical symptoms and the free T4 results remained within reference range. No SAEs or deaths were reported based on these preliminary safety data as of 07 April 2021 and 14 April 2021.

Current evidence indicates the clinical safety profile of PF 07321332 is acceptable at single doses up to 1500 mg alone and up to 750 mg administered with ritonavir (100 mg at -12h, 0h, 12h), and at repeated daily doses administered orally for 10 days of up to 500 mg PF-07321332 BID with 100 mg ritonavir BID.

C4671005 (NCT04960202), a Phase 2/3, randomized, double-blind, placebo-controlled study in nonhospitalized 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/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/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/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/ritonavir was safe and well tolerated.

Results from a protocol-specified interim analysis of Study C4671002 (NCT05011513), which included 45% of the study's planned enrollment, showed that the novel primary endpoint of self-reported, sustained alleviation of all symptoms for 4 consecutive days, as compared with placebo, was not met. However, 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/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).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07321332 may be found in the investigator's brochure, which is the SRSD for this study. The SRSD for the ritonavir is the USPI[41] for NORVIR.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07321332		
Emesis	Sporadic emesis was observed at ≥100 mg/kg/day of PF-07321332 in the 15-day NHP toxicology study.	AEs will be monitored and participants may receive antiemetics.
Hemodynamic and inflammatory effects	Low level inflammation (increase in fibrinogen) in 15-day NHP toxicology study and changes in platelets, globulin and albumin/globulin ratio and coagulation system (increase in PT and aPTT) in 14-day rat toxicology study.	In addition to vital signs and close observation for AEs, fibrinogen, platelets, D-dimer, PT and aPTT, albumin, and total protein will also be monitored. Refer to Section 8.3.8.
TSH elevations	TSH changes observed with the administration of PF-07321332 during study C4671001	TSH and T4 (free) will be monitored. Refer to Section 8.3.8.
Study Intervention(s): 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 twice daily is used in this study. There will be close observation of AEs. In addition to ongoing review of AEs by the sponsor, an E-DMC will review safety data as described in Section 10.1.5.1. Taking study intervention with food may improve tolerability.
Neurological disturbances (eg, paresthesia, including oral paresthesia, dysgeusia and dizziness)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs. 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

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

2.3.2. Benefit Assessment

As of January 2022, no orally administered therapeutic intervention has been approved or received an EUA in the US for use in postexposure/preemptive treatment/prophylaxis, but 2 orally administered antivirals for the treatment of COVID-19 in patients at high risk of progression to severe COVID-19 (eg, Paxlovid[42] and molnupiravir[43]) have begun receiving EUAs (or equivalent) in various regions. Additionally, the emergence of variants such as the omicron variant that may be associated with reduced protection afforded by vaccine and monoclonal antibodies further emphasizes the need for additional treatment and postexposure prophylaxis options.[34,35] On this basis, the potential benefit to individual study participants who receive the study intervention may include preventing development of symptomatic SARS-CoV-2 infection following exposure to a household contact (an index patient) with symptomatic COVID-19. By virtue of participating in the study and ongoing evaluation and assessment for SARS-CoV-2 infection, there is the potential benefit of early detection and subsequent medical management should infection with SARS-CoV-2 be detected.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the seriousness of COVID-19, the lack of readily available postexposure prophylactic treatment options and the measures taken to minimize risk to participants in this study, the potential risks identified in association with PF-07321332 are justified by the anticipated benefits that may be afforded to study participants by preventing development of symptomatic SARS-CoV-2 infection. An independent E-DMC will be responsible for monitoring the safety of participants at regularly scheduled intervals throughout the duration of the study and for assessing efficacy, futility, and sample size re-estimation at the time of the interim analysis according to the E-DMC charter.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test--confirmed SARS-CoV-2 infection through Day 14.	• The risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test--confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline and are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
• To describe the safety and tolerability of 5-day and 10-day regimens of PF-07321332/ritonavir relative to placebo in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	• Incidence of TEAEs • Incidence of SAEs and AEs leading to discontinuation.	• Not applicable.
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection in adult participants who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness: • Proportion of participants with symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. • Proportion of participants with COVID-19 related hospitalization or death from any cause by Day 28.	• The risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test--confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing SARS-CoV-2 infection in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with asymptomatic RT-PCR or rapid antigen test--confirmed SARS-CoV-2 infection through Day 14. • Time to RT-PCR or rapid antigen test--confirmed SARS-CoV-2 infection through Day 14. Of the participants who have a positive RT-PCR result at baseline: • Proportion of participants with symptomatic RT-PCR or rapid antigen test--confirmed SARS-CoV-2 infection through Day 14. Of the participants who have a negative or positive RT-PCR result at baseline: • Proportion of participants with symptomatic RT-PCR or rapid antigen test--confirmed SARS-CoV-2 infection through Day 14.	• Not applicable.
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the duration and	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with no, mild, moderate, or severe	• Not applicable.

Objectives	Endpoints	Estimands
severity of COVID-19 related signs and symptoms in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	signs and symptoms attributed to COVID-19 through Day 28. • Number of days of symptomatic SARS-CoV-2 infection through Day 28.	
• To determine the PK of PF-07321332 in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable.
• To describe all-cause mortality in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with death (all-cause) through Day 38.	• Not applicable.
• To describe the viral load in nasal samples over time in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Viral titers measured via RT-PCR in nasal swabs over time. Of the participants who have a positive RT-PCR result at baseline: • Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.
• To describe hospitalizations in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Number of days of hospital and ICU stay in participants with COVID-19-related hospitalization through Day 28.	• Not applicable.
• To describe COVID-19 related medical visits in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Number of COVID-19 related medical visits through Day 28.	• Not applicable.

4. STUDY DESIGN

4.1. Overall Design

This Phase 2/3, randomized, double-blind, double-dummy, placebo-controlled study will compare the efficacy of 2 regimens of PF-07321332/ritonavir versus placebo in approximately 2880 participants who have a negative screening SARS-CoV-2 rapid antigen test result and are asymptomatic household contacts of individuals who are symptomatic and recently tested positive for SARS-CoV-2 (index case: defined as patient with symptomatic

COVID-19). Index cases may be participants in Phase 2/3 safety and efficacy studies of PF-07321332/ritonavir (C4671002 and C4671005), but this is not required. Eligible participants for this study will be randomly assigned (1:1:1) within 96 hours after collection of the index case's first positive SARS-CoV-2 test to receive:

- PF-07321332/ritonavir q12h for 5 days followed by matching placebo q12h for 5 days; or
- PF-07321332/ritonavir q12h for 10 days; or
- Matching placebo for PF-07321332/ritonavir q12h for 10 days.

Randomization will be stratified based on the presence of risk factors associated with severe COVID-19 illness (see Appendix 11) and geographic region at screening. Throughout the study period, provision will be made to allow study visits to be conducted at a participant's home or at another nonclinic location approved by the investigator where possible when participants are unwilling or unable to attend a clinic visit at the investigational site.

Participants will be screened within 24h before randomization. The total duration of the study is up to 42 days and includes screening, study intervention through Day 10, efficacy assessments through Day 14, and a safety follow-up period through Day 38 [±3 days].

An independent E-DMC will review unblinded data to ensure the safety of participants on an ongoing basis throughout the duration of the study. In addition to up to weekly reviews of safety data, the E-DMC will review the following:

- Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 150 participants have completed Day 10 of the study, at which point enrollment will be paused pending E-DMC review of the safety data. After review of the sentinel cohort, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.
- Interim analysis: An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by an E-DMC after a prespecified accrual of participants (ie, before or at approximately 70% participants have completed the Day 14 assessments with a minimum number of 24 participants having symptomatic infection [mITT analysis set]).

Subsequent to the planned interim analysis, there will be a single analysis for reporting the results of this study after all participants have had their last study visit.

4.2. Scientific Rationale for Study Design

This study evaluates safety and the potential efficacy of an investigational agent on preventing symptomatic SARS-CoV-2 infection (postexposure prophylaxis) in household contacts of individuals who recently tested positive for SARS-CoV-2 and are symptomatic

(ie, index case: patient with symptomatic COVID-19). Prior studies of antiviral, mAb, and antimalarial agents have evaluated the efficacy of these agents as postexposure prophylaxis and/or preemptive treatment for symptomatic SARS-CoV-2 infection. Studies with mAb suggest that post-exposure treatment of asymptomatic patients may reduce symptomatic SARS-CoV-2 infection.[37,44-49]

Efficacy assessments (including collection of nasal swabs and participant-reported COVID-19 symptoms) will be collected through Day 14 and 28, respectively. The symptom endpoint includes those recommended by FDA and relies on symptoms that have been associated with COVID-19, and which are expected to be dynamic and improve with effective anti-SARS-CoV-2 therapy. Nasal swabs will be collected daily through Day 14 to determine if and when participants become RT-PCR positive. Participants who develop signs or symptoms consistent with COVID-19 during the study will undergo an in-person medical assessment including a rapid antigen test to confirm SARS-CoV-2 infection so that the participants may receive SoC therapy as described in Section 6.8. Additional testing may be performed in accordance with local medical practice.

This study uses a randomized, double-blind, double-dummy, placebo-controlled design, which is a well-accepted approach for evaluating efficacy in a clinical research setting.

4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants to ensure the study population is representative of the patient population that will be treated with PF-07321332/ritonavir in clinical practice.

4.2.2. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of PF-07321332 have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.3. Collection of Retained Research Samples

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

4.3. Justification for Dose

Dosing regimens of 300 mg PF-07321332 coadministered with 100 mg ritonavir q12h administered orally for 5 days or 10 days will be evaluated in this study. Dose selection for this study included consideration of all relevant available preclinical and clinical data, including repeat-dose toxicology studies, clinical safety, and PK data from the Phase 1 study (C4671001), and *in vitro* pharmacology studies with PF-07321332.

A preliminary population PK model was developed from the Phase 1 (C4671001) PK data. Following a first dose of 300 mg PF-07321332 coadministered with 100 mg ritonavir q12h, median C_{trough} of unbound (free) PF-07321332 is predicted to be approximately 289 ng/mL (equivalent to 933 ng/mL total), ie, approximately 3-fold higher than the in vitro EC_{90} of

90.4 ng/mL determined in dNHBE cells (equivalent to 181 nM, f_u, human=0.310). At this dose, for a hypothetical intersubject variability of 60%, more than 95% of the participants are predicted to maintain free PF-07321332 concentrations above the in vitro EC_{90} over the 12- hour dosing interval.

Based upon epidemiological characteristics of SARS-CoV-2[29] and assuming a range of different scenarios related to the timing of initiation of treatment for the household contact relative to the timing of exposure to the index case or relative to the onset of symptoms for the index case, simulations using a previously published QSP model[50] were performed to advise on the potential impact of different treatment durations on the viral load for household contacts.

Based upon these simulations, initiation of treatment for household contact nearer to the timing of exposure or onset of symptoms for the index case suggest some possibility for shorter treatment durations to be associated with an increase of the viral load of household contacts after completion of the treatment regimen. Although modeling simulations suggest some potential for an increase of the viral load of household contacts after completion of the treatment regimen, there is supportive evidence that a shorter treatment may be effective in the setting of post-exposure prophylaxis. More specifically, the viral epidemiology characteristics of SARS-CoV-2 are considered to be similar to the characteristics of influenza and recently, a 5-day treatment regimen of oseltamivir was shown to be non-inferior to a 10-day treatment regimen in post-exposure prophylactic treatment of hospitalized patients exposed to influenza and not immediately isolated from the index case.[51]

Considering the uncertainty of the potential impact of treatment duration on providing effective post-exposure prophylaxis in household contacts exposed to persons with COVID-19, the efficacy and safety of 5- and 10-day treatment durations will be assessed in this study.

Preliminary safety data from study C4671001, collected up to 07 April 2021 for PART-1 and 14 April 2021 for PART-2, showed an acceptable safety profile for single doses of PF-07321332 ranging from 150 mg to 1500 mg dosed alone and of 250 mg and 750 mg dosed with ritonavir (100 mg administered at -12h, 0h, 12h) and for 10 day repeated doses ranging from 75 mg BID to 500 mg BID with 100 mg ritonavir BID.

The proposed dosing regimens of 300 mg PF-07321332 coadministered with 100 mg ritonavir q12h administered orally for 5 or 10 days is thus expected to be safe and efficacious.

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 he/she has 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. Use of a pre-screener for study recruitment purposes 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 screening visit.

   - WOCBP may be enrolled.

   - All fertile participants must agree to use a highly effective method of contraception. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

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

3. Participants who have a negative screening SARS-CoV-2 rapid antigen test result and who are asymptomatic household contacts (ie, living in the same residence, see Appendix 13) of an individual who is symptomatic and recently tested positive for SARS-CoV-2 (ie, index case: patient with symptomatic COVID-19). To be included in the study, participants must be randomized within 24 hours of their negative SARS-CoV-2 rapid antigen test and within 96 hours of collection of the index case's first positive SARS-CoV-2 test.

   Note: The index case will have confirmation of SARS-CoV-2 infection by RT-PCR or other molecular or antigen tests that detect viral RNA or protein (see Section 8.1.5).

Note: Participants with a negative screening SARS-CoV-2 local rapid antigen test result and whose baseline RT-PCR result is returned as positive would be allowed to remain on treatment in the study.

Note: Asymptomatic is defined as having no signs/symptoms consistent with COVID-19 and symptomatic is defined as having at least 1 of the specified signs or symptoms consistent with COVID-19 (see Appendix 9).

Informed Consent:

4. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. History of SARS-CoV-2 infection as determined by a molecular test (antibody, antigen, or nucleic acid) from any specimen collected within 6 months before or during the screening visit.

2. Experiencing measured fever (documented temperature >38˚C or 100.4˚F) or other signs or symptoms consistent with COVID-19 (see Appendix 9).

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

4. CKD or have known moderate to severe renal impairment.

5. Known HIV infection with viral load >400 copies/mL within the last 6 months or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit) (see Appendix 8).

6. Suspected or confirmed concurrent active systemic infection that may interfere with the evaluation of response to the study intervention.

7. Active cancer requiring treatment, with prohibited medication (Appendix 8) that must be administered/continued during the trial period.

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

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

10. 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:

11. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir (see Appendix 8).

12. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment (see Appendix 8).

13. Has received approved, authorized, or investigational anti-SARS-CoV-2 mAb, convalescent plasma, other drugs for treatment of COVID-19, or other anti-SARS-CoV-2 biologic products within 6 months of screening.

14. Has received any SARS-CoV-2 vaccine (includes any level of vaccination) within 6 months prior to screening or is expected to receive a SARS-CoV-2 vaccine or other approved, authorized, or investigational postexposure prophylaxis treatments through Day 38.

15. 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 visit.

Prior/Concurrent Clinical Study Experience:

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

17. Known or prior participation in this trial or another trial involving PF-07321332.

Diagnostic Assessments:

18. Participants with known history of any of the following abnormalities in clinical laboratory tests (within 6 months of the screening visit):

    - AST or ALT level ≥2.5 X ULN;

- Total bilirubin level ≥2 X ULN (≥ 3X ULN for Gilbert's syndrome);
- eGFR <45 mL/min/1.73 m^2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula[52]
- Absolute neutrophil count <1,000/mm^3.
- Note: If the investigator suspects the participant may have any of the above laboratory values, confirmatory tests should be performed at screening to confirm eligibility before the first dose of study intervention. See Appendix 2 for more details.

Other Exclusions:

19. Females who are pregnant or breastfeeding.

20. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

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

5.4. Screen Failures

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

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

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

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to PF-07321332 150 mg tablets and matching placebo and ritonavir 100 mg capsules and matching placebo.

6.1. Study Intervention(s) Administered

Study Interventions(s)				
Intervention Name	PF-07321332	Placebo for PF-07321332	Ritonavir	Placebo for Ritonavir
ARM Name (group of patients receiving a specific treatment (or no treatment)	PF-07321332/ritonavir	Placebo	PF-07321332/ ritonavir	Placebo
Type	drug	placebo	drug	placebo
Dose Formulation	tablet	tablet	capsule	capsule
Unit Dose Strength(s)	150 mg	0 mg	100 mg	0 mg
Dosage Level(s)	300 mg	0 mg	100 mg	0 mg
Route of Administration	oral	oral	oral	oral
Use	experimental	placebo	experimental	placebo
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IP manual.	Provided centrally by the sponsor. Refer to the IP manual.	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 blister wallets. Each wallet will be labeled as	Study intervention will be provided in	Study intervention will be provided in HDPE bottles. Each bottle will be labeled	Study intervention will be provided in

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

Study Arm(s)			
Arm Title	PF-07321332/ritonavir (5-Day)	Placebo	PF-07321332/ritonavir (10-Day)
Arm Type	experimental	placebo	experimental
Arm Description	Participants will receive PF-07321332/ritonavir 300 mg/100 mg q12h from Day 1 through Day 5 followed by 0 mg/0 mg q12h from Day 6 through Day 10.	Participants will receive 0 mg/0 mg q12h for 10 days from Day 1 through Day 10.	Participants will receive PF-07321332/ritonavir 300 mg/100 mg q12h for 10 days from Day 1 through Day 10.
Associated Intervention Labels	PF-07321332/ritonavir and Placebo for PF-07321332 /Placebo for Ritonavir	Placebo for PF-07321332 and Placebo for Ritonavir	PF-07321332/ritonavir

6.1.1. Administration

PF-07321332 150 mg tablet or placebo for PF-07321332 will be administered with ritonavir 100 mg or placebo for ritonavir capsule for 10 days. Participants will be dispensed:

- 2 tablets of PF-07321332 150 mg or placebo for PF-07321332 (single tablet from each blister cell, one at a time) q12h
- 1 capsule of ritonavir 100 mg or placebo for ritonavir q12h.

Participants should take the first dose of study intervention on Day 1, preferably during the in-person visit; that is, participants should take 2 tablets of PF-07321332 150 mg or placebo and 1 capsule of ritonavir 100 mg or placebo at the same time and no more than 10 minutes apart. To allow the participant to select a convenient 12-hour dosing schedule, timing of dosing for the second dose may be adjusted slightly, but should be taken at least 4 hours but no later than 12 hours after the first dose. The remaining doses should be taken every 12 hours [±30 minutes]. Participants will swallow the study intervention whole and will not

manipulate or chew the study intervention prior to swallowing. Participants may take the study intervention with or without food. Taking study intervention with food may improve tolerability. Refer to the IP Manual for additional dosing and administration instructions.

If a dose is delayed, it should be taken as soon as possible, but no later than 4 hours before the next scheduled dose. Participants should not double up the next dose of study intervention in order to "make up" what had been missed. Dosing should be stopped at the end of the treatment period. Any remaining tablets and/or capsules at the end of 10 days (or 11 days if only one dose was administered on Day 1) should be returned.

6.2. Preparation, Handling, Storage, and Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business. Study intervention may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments and the chain of custody of study intervention must be kept in the participant's source documents/medical records. For investigational sites using ground transportation to deliver study intervention to participants, stability data reveal that if the total duration of transit is less than 24 hours, temperature monitoring is not required.

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

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

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

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

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

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

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

6.2.1. Preparation and Dispensing

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

Study intervention and placebo will be dispensed by qualified blinded site personnel according to the IP manual. The study intervention will be administered in a blinded fashion to the participants.

Study intervention will be dispensed as noted in the SoA.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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

Returned study intervention must not be redispensed to the participants.

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

6.3.2. Blinding of the Sponsor

The majority of sponsor staff will be blinded to study intervention allocation. There will be an unblinded team supporting the interactions with, and the analyses for, the E-DMC while the study is ongoing. The team will consist of clinicians, statistician(s), and programmer(s) and will be separate from the blinded members of the study team.

The study will be unblinded at the group and participant level after all participants complete the Day 38 visit (or ET prior to Day 38 visit). However, if efficacy is demonstrated at the interim analysis, an unblinded submissions team may be assembled to prepare unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing.

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

6.3.3. Breaking the Blind

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

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

6.4. Study Intervention Compliance

Participants will be issued an electronic study intervention diary (ie, participant-completed study intervention log) or may use an application installed on their device and will be educated to record the date and time of their study intervention dosing preferably at the time of first dose.

Compliance with study intervention will be assessed by delegated site personnel through the accounting of unused study intervention returned by the participant at the study visits, review of the electronic study intervention diary, and discussion with the participant.

Study intervention administration, including any deviation(s) from the prescribed dosage regimen, should be recorded in the CRF.

A record of the number of study intervention tablets/capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

The following noncompliance cases will be considered medication errors (See Section 8.3.10):

- Participants interrupting study intervention for 2 consecutive doses;
- Participants taking either PF-07321332 or ritonavir alone for 2 consecutive doses.
- Participants who have an overall study intervention compliance of <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 and ensure steps are taken to improve compliance.

6.5. Dose Modification

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

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

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

6.7. Treatment of Overdose

For this study, any dose of PF-07321332 greater than 900 mg or ritonavir greater than 300 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study intervention (whichever is longer).

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

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

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

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

6.8. Concomitant Therapy

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

Permitted During the Study

All participants who develop confirmed COVID-19 may continue study intervention and may receive SoC therapy including products authorized under an Emergency Use Authorization (or equivalent in countries where the study is being conducted) where appropriate, in addition to study intervention, unless listed as prohibited medication (see below and Appendix 8). Discontinuation of study intervention is at the investigator's discretion. However, if the investigator decides to administer SoC therapy for COVID-19 that is prohibited for DDI reasons, the participant must discontinue study intervention but should continue in the study. 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. The investigator should ensure that any recommended SoC therapy is not a strong inducer of CYP3A4 or highly dependent on CYP3A4 for clearance if it is planned to be administered concomitantly with study intervention.

In countries in which therapiesare are authorized or approved for the treatment of COVID-19, all participants who develop confirmed COVID-19 disease will be referred locally for treatment as deemed appropriate by the investigator (see above) and local guidelines. This referral should be documented. Notwithstanding, this treatment is not mandatory for participation in this study.

Prohibited During the Study

Participants may not receive therapeutics, drugs, or vaccines described in the exclusion criteria (see Section 5.2), antiviral treatment for COVID-19 (eg, molnupiravir, Paxlovid) or listed as prohibited medications (see Appendix 8) during the study period with the exceptions described above for participants who develop confirmed COVID-19.

PF-07321332 and ritonavir are both primarily metabolized by cytochrome P450 (CYP) 3A4. Therefore, concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to dosing of study intervention and during study treatment.

Additionally, PF-07321332 and ritonavir are inhibitors of CYP3A4. Therefore, medications highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events are not permitted during dosing of PF-07321332/ritonavir and for 4 days after the last dose of PF-07321332/ritonavir. Because ritonavir 100 mg every 12 hours is being used to boost the exposure of PF-07321332, no additional DDIs are expected other than those associated with ritonavir 100 mg q12h based on in vitro assessments.

A nonexhaustive list of prohibited and precautionary medications is provided in Appendix 8. If a medication is not listed, it should not automatically be assumed it is safe to coadminister. Appropriately qualified site staff will review all concomitant medications to determine if they are strong inducers of CYP3A4 or highly dependent on CYP3A4 for clearance, and thus prohibited.

6.8.1. Rescue Medicine

Standard medical supportive care may be provided to manage AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- AE (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;
- Hospitalization during the active treatment period;

- Miss more than 2 consecutive doses of study intervention.

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

7.1.1. Potential Cases of Decreased eGFR

If postcreening eGFR is <45 mL/min/1.73m^2, the participant will be instructed to discontinue any remaining study intervention doses as soon as study staff become aware of laboratory results.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

The following actions must be taken if a participant fails to 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, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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, blood count) 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 may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

The total blood sampling volume for individual participants in this study is approximately 183 mL. There will be an additional optional 1 mL of blood collected for a subset of participants who agree to self collect an optional PK sample (Tasso device). 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. Efficacy Assessments

8.1.1. Participant Diary

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

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

The diary allows recording of these assessments only within a fixed time window (eg, 24h), thus providing an accurate representation of the participant's experience at that time. The participant is able to make revisions to incorrect entries before pressing the save or submit button. In the event that a participant becomes aware of an error in data after the entry is saved, a change to the diary data may only be made by the investigator submitting a data clarification form. Data reported in the participant diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the sponsor or delegate at all times via an internet-based portal.

8.1.2. Daily Signs and Symptoms of COVID-19

On Day 1, participants will complete the study diary before receiving study intervention. Participant assessment of COVID-19-related symptoms should be recorded at approximately the same time each day as specified in the SoA and as described in Section 8.1.1.

COVID-19-related symptoms will be evaluated in accordance with FDA guidelines (Appendix 9).[53] Participants will record a daily severity rating of their symptoms over the past 24 hours based on a 4-point scale in which 0 is reported if no symptoms were present; 1 if mild; 2 if moderate; and 3 if severe.

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

Sense of smell and sense of taste will each be rated on a 3-point Likert scale where 0 is reported if the sense of smell/taste was the same as usual, 1 if the sense of smell/taste was less than usual, and 2 for no sense of smell/taste. Investigators will instruct participants to contact them if they develop signs/symptoms of COVID-19 – to inform them of their symptoms and to schedule a COVID-19 Signs/Symptoms Onset visit as soon as possible, but no later than 2 days after symptom onset, as specified in the SoA. Investigators will instruct symptomatic participants to follow local public health measures to reduce the spread of COVID-19.

8.1.3. COVID-19 Related Medical Visit Details

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

If the participant has a COVID-19 Signs/Symptoms Onset visit, this must be reported as a COVID-19 related medical visit.

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

8.1.4. Oxygen Support Details

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

8.1.5. Index Case Characteristics

Index cases will be determined through interview with the C4671006 study participant. The index case may be a participant in the C4671002 or C4671005 studies, but this is not required. However, minimum data as outlined below must be collected for confirmation of the C4671006 study participant's status as a household contact and the exposure period.

The following information about the index case will be collected through interview with the study participant:

- Date of index case SARS-CoV-2 infection diagnosis (sample collection date of first positive test);
- Date of onset of COVID-19 symptoms.

The following information about the index case will be collected through interview with the study participant to characterize the exposure period. For index cases who are participants in the C4671002 or C4671005 study, this information will be collected in those studies. If the index case is not a participant in the C4671002 or C4671005 study, this information will only be collected if available and permitted by local laws and regulations:

- Age;
- Whether the index case received vaccination or treatment for COVID-19 prior to or during the exposure period;
- Whether the index case was isolated from the study participant after the initial exposure;
- Relationship of the index case to the study participant (spouse, parent, son/daughter, etc);
- Does the index case sleep in the same room as the study participant.

8.1.6. Household Characteristics

Household characteristics will be determined through interview with the C4671006 study participant and may be updated during the study. This assessment will support the characterization of the exposure period and may be relevant for interpretation of efficacy data. The household characteristics include:

- Number of people living in household;
- Number of additional confirmed SARS-CoV positive or suspected (ie, symptomatic) household members;
- Number of other household contacts in this residence who are participants in this study or receiving another COVID-19 treatment.

8.1.7. PRO Assessments

8.1.7.1. WPAI

COVID-19 impacts manual and office-based work, and results in missed work due to illness or quarantine and loss in productivity.[54] The WPAI-GH is being implemented for COVID-19 (ie, WPAI-COVID-19) in order to evaluate change from baseline in work burdens. The WPAI-GH has demonstrated validity, reliability and sufficient predictive value to measure the impact of disease on absenteeism, presenteeism, and overall productivity in a manner that can also be monetized.[55]

8.1.7.2. EQ-5D-5L Scale

The EQ-5D is a validated, standardized, generic instrument that is a preference-based health related quality of life questionnaire in cost effectiveness and HTA.[56-58] Recently, a version was developed called EQ-5D-5L with 5 response levels on each dimension.[56-62]

Measurement properties of the EQ-5D-5L demonstrated to be a valid version of the 3 level questionnaire that improved measurements by adding discriminatory power, reducing the ceiling, and establishing convergent and known groups validity.[56,58,60,61] Both the EuroQol EQ-5D-3L and EQ-5D-5L versions are well established instruments used to measure health

states and utilities in various diseases areas and assess mobility, self care, usual activities, pain/discomfort, anxiety/depression and health status using a VAS.[59,63] The EQ-5D-5L should be completed as described in the SoA.

8.1.7.3. Global Impression Questions

For participants who report COVID-19 symptoms in the diary, 3 additional questions will be included in the ePRO to assess patient-reported global impression items: a) return to usual health; b) return to usual activities; and c) overall COVID-19-related symptoms.[53]

8.2. Safety Assessments

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

8.2.1. Medical History

Medical history (including prior documented infection) and demographics will be collected at screening. Smoking status will be collected. Complete medication history of all prescription or nonprescription drugs (including vaccinations), and dietary and herbal supplements taken within 30 days prior to the planned first dose will be collected.

Risk factors for the study participant developing severe COVID-19 illness will be recorded (Appendix 11).

8.2.2. Height and Weight

Height and weight will also be measured and recorded at screening. Height may be self-reported.

8.2.3. Targeted Physical Examinations

A targeted physical examination will include, at a minimum, cardiopulmonary assessments. Investigators should pay special attention to any previously identified or new AE/targeted condition that the participant has experienced.

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 8.3.1 to 8.3.3.

8.2.4. Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed as specified in the SoA. In addition to this, participants attending a COVID-19 Signs/Symptoms Onset visit will also have oxygen saturation measured.

Blood pressure and pulse rate measurements will be assessed with the participant in the supine or seated position with their feet on the floor when possible with a completely automated device. It is recommended that the same position should be used for a participant throughout the study duration. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Investigators will supply each participant with a thermometer and will instruct them to measure their temperature if they are feeling feverish. Investigators will instruct participants to contact them if they develop a fever (>100.4˚F or >38˚C), to inform them of their fever and to schedule a COVID-19 Signs/Symptoms Onset visit as soon as possible but no later than 2 days after symptom onset, as specified in the SoA. Investigators will instruct participants with fever to follow local public health measures to reduce the spread of COVID-19.

Each participant will also be supplied with a pulse oximeter to be used at home as directed by the investigator. This may include monitoring of oxygen saturation for participants who develop COVID-19 symptoms and will be implemented at the discretion of the investigator. The investigator will instruct the participant regarding use of the pulse oximeter and what value should trigger a call to the investigator.

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

8.2.5. 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 the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events,[64] version 2.1. 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

If a baseline laboratory result meets Section 5.2 exclusionary laboratory values and the participant is still receiving study treatment, the investigator should contact the Medical Monitor. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. 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) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records. If the pregnancy test is positive, the EDP should be reported (Section 8.3.5.1). Confirm that the participant is adhering to the contraception method(s) required in the protocol.

8.3. 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 8.3.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including 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 and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-Up of AEs and SAEs

After the initial AE 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 given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities 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.

8.3.5. 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 exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental 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 exposes his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 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 CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

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

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.5.3. Occupational Exposure

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

AESIs include hemodynamic events, inflammatory events, and thyroid-related events.

Adverse events of special interest (AESIs) are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- The administration of expired study intervention
- The administration of an incorrect study intervention
- The administration of an incorrect dosage
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use
- The administration of study intervention consistent with the medication error descriptions in Section 6.4.

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

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if

applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Pharmacokinetics

Blood samples of approximately 4 mL, to provide a minimum of 2 mL plasma, will be collected for measurement of plasma concentrations of PF-07321332 as specified in the SoA. Self-collected whole blood (Tasso device) may also be collected and used to measure concentrations of PF-07321332. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples obtained ≤1 hour outside the scheduled nominal sampling time windows will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of PF-07321332. Samples collected for analyses of PF-07321332 concentration 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, or for research related to the study intervention(s) and COVID-19. Samples may also be used to evaluate the PK of ritonavir.

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

Samples collected for measurement of concentrations of PF-07321332 will be analyzed using a validated analytical method in compliance with applicable SOPs. CCI [redacted] CCI [redacted]

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

Drug concentration information that would unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

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

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8.6. Biomarkers

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

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

- Nasal swab will be collected to measure SARS CoV-2 viral load by RT-PCR.
- Nasal viral load samples may be used for SARS CoV-2 viral sequencing.
- Nasal viral load samples may be used for SARS CoV-2 infectivity assays and phenotypic analyses.
- 10 mL blood optimized for plasma may be utilized for proteomics and immunologic studies.

8.6.1. Specified Gene Expression (RNA) Research

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

8.6.2. Specified Protein Research

Blood will be collected for plasma biomarkers as specified in the SoA and may be used for proteomics, immunologic studies, as well as markers associated with coagulation, organ or

endothelial cell dysfunction. Storage and shipping instructions will be in accordance with the laboratory manual.

8.6.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.6.4. SARS-CoV-2 Assessments

8.6.4.1. Rapid Antigen Assessments

Rapid antigen testing for SARS-CoV-2 will be performed as described in the SoA. Investigator sites will use test kits that are authorized for use in this study.

8.6.4.2. Viral Load Assessments

The first nasal swab will be self collected by the participant under observation by site staff to ensure correct collection methodology. Thereafter, nasal swabs will be collected by the HCP or self collected by the participant as specified in the SoA. On the days where there is an in-person visit, the nasal swab should be collected by the HCP and the participants instructed to not collect the nasal swab prior to the visit. If, for any reason, a nasal swab was already collected in the morning of an in person visit, another swab for viral load assessment should not be collected on the same day and that would not be considered a protocol deviation.

Additional swabs may be required at the visit on days for which an in-person visit occurs (eg, COVID-19 Signs/Symptoms Onset visit), which should be collected by the HCP if not already self collected by the participant.

Results of centrally read nasal swabs will not be available to the investigator. Therefore if COVID-19 symptoms occur during the study, investigators will make treatment decisions based on assessment of the participant's symptoms, rapid antigen testing results, other locally available testing results (eg, RT-PCR) obtained and used outside this trial, and other relevant factors determined in the investigator's clinical judgment. Results of these local tests will be recorded on the CRF.

Nasal swabs will be collected per the SoA, and may be analyzed to measure SARS-CoV-2 RNA by RT-PCR. CCI

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Storage and shipping instructions will be in accordance with the laboratory manual.

8.6.5. Assessments for Other Respiratory Pathogens

Nasal swabs that are collected as specified in the SoA may be sent to be analyzed for presence of SARS-CoV-2. Samples from symptomatic participants negative for SARS-CoV-

2 will undergo qualitative assessment for presence of influenza or RSV. As stated above, results of centrally read nasal swabs may not be immediately available to the investigator.

Participants who experience symptoms consistent with COVID-19 after the nasal swab collection period described in the SoA will undergo local testing for SARS-CoV-2 infection and other respiratory infections, per local standard of care. Results of these tests will be recorded in the CRF.

8.6.6. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

- 10 mL blood optimized for serum isolation Prep B2

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.

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

Health economics/medical resource utilization and health economics parameters will be evaluated in this study (Section 8.1.2. and Section 8.1.3).

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

The primary hypothesis is to test, in participants who have a negative RT-PCR at baseline, whether or not the risk ratio between 5-day and 10-day regimens of PF-07321332/ritonavir

versus placebo in the proportion of participants who develop symptomatic RT-PCR or rapid antigen test-confirmed infection through Day 14 is equal to 1:

Null hypothesis: H_0 $\frac{\pi_{PF-073211332}}{\pi_{placebo}} = 1$

Alternative hypothesis: H_a $\frac{\pi_{PF-073211332}}{\pi_{placebo}} \neq 1$

Where $\pi_{PF\text{-}07321332}$ versus $\pi_{placebo}$ are the symptomatic infection rate through Day 14 for 5-day and 10-day regimens of PF-07321332 /ritonavir versus placebo groups in participants who have a negative RT-PCR result at baseline.

9.1.1. Estimands

9.1.1.1. Primary Estimand/Co-Primary Estimands

The primary estimand is the risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline and are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.

9.1.1.2. Secondary Estimand

The estimand associated with the secondary objective is

- The risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test-confirmed SARS CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.

Symptomatic RT-PCR or rapid antigen test-confirmed infection through Day 14 is considered the main clinical outcome measure so estimands for the measure in targeted populations are presented. Estimands for the other outcome measures/populations are considered supportive of the main outcome measures and are not presented.

9.1.2. Multiplicity Adjustment

There will be 2 group comparisons for the primary endpoint: 5-day regimen of PF-07321332/ritonavir versus placebo groups and 10-day regimen of PF-07321332/ritonavir versus placebo groups. Multiplicity adjustment for the primary endpoint will be made for multiple comparisons using Hochberg method.[65]

Following the positive test of the primary endpoint, the key secondary endpoint will be tested sequentially: proportion of participants with symptomatic RT-PCR or rapid antigen

test-confirmed SARS-CoV-2 infection through Day 14 in participants who have a negative RT-PCR result at baseline and are at increased risk of severe COVID-19 illness.

If the primary endpoint is significant for both treatment groups, the key secondary endpoint will be tested at full alpha level using Hochberg method[65] to adjust for multiple comparisons for both treatment groups.

If one of PF-07321332/ritonavir arms is discontinued, sequential testing will be performed in the remaining PF-07321332/ritonavir arm in the order of primary endpoint and the key secondary endpoint. Details will be provided in the SAP or interim analysis plan.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Full Analysis Set (FAS)	All participants randomly assigned to study intervention.
Safety Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they received.
Modified Intent-To-Treat (mITT)	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and have a negative RT-PCR result at baseline. Participants will be analyzed according to the study intervention they were randomized.
Modified Intent-To-Treat1 (mITT1)	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and have a positive RT-PCR result at baseline. Participants will be analyzed according to the study intervention they were randomized.
Modified Intent-To-Treat2 (mITT2)	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and have a negative RT-PCR result at baseline and are at increased risk of severe COVID-19 illness. Participants will be analyzed according to the study intervention they were randomized.

Participant Analysis Set	Description
Per-Protocol (PP)	All participants in the mITT set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint. Protocol deviations will be reviewed to generate the list of participants with significant deviations to be excluded from the PP analysis set. The PP exclusion criteria will be finalized prior to breaking the blind.

9.3. Statistical Analyses

The SAP will be developed and finalized before 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

The number of participants randomized to the double-blind treatment phase, completing the study drug administration, and completing the study will be summarized from the FAS. The reason for discontinuations will be summarized by treatment group.

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

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

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

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

Time to event will be summarized graphically using Kaplan-Meier plots for each of the treatment groups. Treatment comparisons will be conducted using Cox proportional hazard model.

Below are the combinations of RT-PCR and rapid antigen test results that may be available for a participant and how these results would be considered toward confirming SARS-CoV-2 infection in analyses of the primary and relevant secondary endpoints.

- the first instance of a positive RT-PCR with either a positive or negative rapid antigen test, or
- the first instance of a positive rapid antigen test with a negative RT-PCR test.

If only 1 test is available, infection is defined as a positive result (RT-PCR or rapid antigen test).

Considering the frequency (daily Days 1-14 and at COVID-19 signs and symptoms onset visits) and greater sensitivity for RT-PCR testing relative to the rapid antigen test, it is anticipated that the majority of primary endpoint events will be confirmed with a positive RT-PCR result.

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

The primary efficacy analysis will be conducted using the mITT analysis set.

For the primary efficacy analysis, GEE will be used to analyze the proportion of participants with a negative RT-PCR result at baseline who develop a symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for each treatment group. The compound symmetry variance-covariance structure will be used to account for the correlation among the participants associated with the same index case. The risk ratio between 5-day regimen of PF-07321332/ritonavir versus placebo group and 10-day regimen of PF-07321332/ritonavir versus placebo group and the corresponding 95% CIs will be calculated based on the GEE model using a log link function. Comparisons between the 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo will be presented as a risk reduction with 95% CIs, which is calculated as 1 minus the risk ratio.

A symptomatic infection event is defined as having any SARS-CoV-2 symptoms 1 day prior to, on, or after the first RT-PCR or rapid antigen test-confirmed infection. For COVID-19 related hospitalization or COVID-19-related death, it will be considered as achieving the event.

Multiplicity adjustment for primary endpoint will be made for multiple comparisons using Hochberg method. [65]

Significance level will be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall type I error rate is maintained at 5% (2-sided).

Sensitivity analyses will be performed to the primary efficacy endpoint using PP analysis set.

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

The key secondary efficacy endpoint is:

- the proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adult participants who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness.

The analyses will be performed similarly to the primary efficacy analysis using mITT2 population.

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

- Incidence of TEAEs.
- Incidence of SAEs and AEs leading to discontinuation.
- Proportion of participants with COVID-19 related hospitalization or death from any cause by Day 28 in adult participants who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness.
- Proportion of participants with asymptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for participants who have a negative RT-PCR result at baseline.
- Time to RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for participants who have a negative RT-PCR result at baseline.
- Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in participants who have a positive RT-PCR result at baseline.
- Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for participants who have either a negative or positive RT-PCR result at baseline.
- Proportion of participants with no, mild, moderate, or severe signs and symptoms attributed to COVID-19 through Day 28 for participants who have a negative RT-PCR result at baseline.
- Number of days of symptomatic SARS-CoV-2 infection through Day 28 for participants who have a negative RT-PCR result at baseline.
- PF-07321332 PK in plasma and whole blood (if feasible).
- Proportion of participants with death (all-cause) through Day 38 for participants who have a negative RT-PCR result at baseline.
- Viral titers measured via RT-PCR in nasal swabs over time for participants who have a negative RT-PCR result at baseline.

- Viral titers measured via RT-PCR in nasal swabs over time for participants who have a positive RT-PCR result at baseline.
- Number of days of hospital and ICU stay in participants with COVID-19-related hospitalization through Day 28 for participants who have a negative RT-PCR at baseline.
- Number of COVID-19 related medical visits through Day 28 for participants who have a negative RT-PCR at baseline.

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

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9.3.6. Other Safety Analyses

Safety analyses will be carried out for the Safety population.

The safety assessments include AEs, laboratory assessments, physical examinations, and vital signs. No formal statistical analysis will be conducted on any of the other safety data listed above.

9.3.6.1. Laboratory

Clinical laboratory data will be subjected to clinical review, summarized by frequency of events and mean changes from baseline.

9.3.6.2. Physical Examination and Vital Signs

Physical examination and vitals will be descriptively summarized by treatment group.

9.3.7. Other Analyses

Pharmacogenomic or biomarker data from Retained Research Samples (Section 8.5.2 and Section 8.6.5) may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

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

9.3.7.1. PK Analyses

Descriptive statistics and graphical summaries of PF-07321332 concentrations will be generated. PK samples will be collected as described in the SoA. Additional PK sampling may be self collected in a subset of participants using Tasso, if feasible. Ritonavir concentrations may also be reported. PK data from this study may be combined with other studies and analyzed using population PK approaches. Results from any population PK analyses will be reported outside of the clinical study report.

9.4. Interim Analyses

An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by an independent E-DMC after a prespecified accrual of participants (ie, before or at approximately 70% overall participants have completed the Day 14 assessments with a minimum number of 24 participants having symptomatic infection [mITT analysis set]). The nominal significance level for the interim and final analyses is determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary, with an overall two-sided type I error rate of 5%. O'Brien-Fleming approach provides relatively conservative stopping boundary for decision making, ie, the nominal level for interim analysis for efficacy and futility is 0.014 and 0.32. The nominal significance level for final analysis is 0.046. The actual stopping boundaries will depend on the exact number of participants included in the interim analysis.

At the predefined interim analysis, the sample size may be adjusted based on sample size re-estimation with maximum increase of 30%. A well-established method such as CHW[66] will be used to control the Type I error probability. Besides stopping a PF-07321332/ritonavir arm for safety or futility, a PF-07321332/ritonavir arm (5-day or 10-day regimen) may be discontinued based on overall evaluation of efficacy and safety profiles between the 2 arms.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in a DMC charter. In addition, the analysis details will be documented and approved in the SAP.

9.5. Sample Size Determination

Based on the results from Study C4671005, which showed PF-07321332/ritonavir treatment significantly reduced the risk of hospitalization or death from any cause by 89% compared with placebo in nonhospitalized symptomatic adult participants with COVID-19 who were at increased risk of progression to severe disease when they were treated within 3 days of symptom onset, and the high relative risk reduction (approximately 80%) observed in Regeneron REGEN-COV post-exposure prophylaxis study, the risk reduction between PF-07321332/ritonavir group versus placebo group is assumed to be 70%. The symptomatic infection rate assumption in the placebo group is adjusted to 4% based on the observed seropositivity rate in this study and the impact of seropositivity on the incidence of primary endpoint events in the REGEN-COV post-exposure prophylaxis study where the incidence of symptomatic infection was 2% in participants who were seropositive and 8% in those who were seronegative.[2] As of January 2022, a large percentage of participants were observed to be seropositive. Based on a 2% placebo event rate for participants who were seropositive and 8% placebo rate for participants who were seronegative observed in the REGEN-COV postexposure prophylaxis study,[2] the expected placebo rate across the 2 groups is estimated to be approximately 3%. In addition, based upon emerging epidemiology data for the Omicron variant,[34] which suggests higher infectivity than with prior variants, the placebo rate is adjusted to be 4%.

Among baseline RT-PCR negative participants, assuming a 4% symptomatic infection rate in the placebo group, a 70% reduction in symptomatic infection (1.2% symptomatic infection rate) in the PF-07321332/ritonavir group (5-day and 10-day regimen), a sample size of 821 participants per group (2463 participants total) will provide approximately 90% power for each comparison between 5-day and 10-day regimens of PF-07321332/ritonavir group versus placebo group under a 2-sided type-1 error rate of 5%. Assuming approximately 5% of participants with negative rapid antigen test result at screening will have a positive RT-PCR result at baseline, and assuming an approximately 10% dropout rate, the total sample size for this study will be approximately 2880 participants.

Study enrollment will stop once approximately 2463 participants are evaluable and at least 34 participants had symptomatic infection for the primary analysis. However, enrollment may continue until the 70% interim analysis has been completed.

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 (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her 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 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 study participant or his or her 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 his or her legally authorized representative must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or his or her legally authorized representative.

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

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

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

Participants or his or her legally authorized representative must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

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

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

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her 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.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

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

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

In addition to up to weekly reviews of safety data, the E-DMC will review the following:

- Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 150 participants have completed Day 10 of the study, at which point enrollment will be paused pending E-DMC review of the safety data. After review of the sentinel cohort, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.

- Interim analysis: An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by the E-DMC after a prespecified accrual of participants (ie, before or at approximately 70% overall participants have completed the Day 14 assessments with a minimum number of 24 participants having symptomatic infection events [mITT analysis set]).

The E-DMC will review all deaths that occur during the study. A pause in enrollment pending E-DMC review will occur if 2 participants experience a Grade 4 or higher AE that is deemed related to study intervention as determined by the investigator and if the sponsor agrees.

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, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for

Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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 retain 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 monitoring plan, 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.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP 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. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

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

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor 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- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. Sponsor’s Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (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 investigator, site staff, and study team. The ECC is to be used by healthcare

professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 1. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Other	Additional Tests (Needed for Hy's Law)
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN or urea Creatinine [a] Glucose Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein	Ferritin hsCRP Procalcitonin LDH CK Haptoglobin <u>Thyroid function</u> TSH T4 (free) <u>Coagulation</u> PT/aPTT Fibrinogen D-dimer <u>SARS-CoV-2 serology</u> IgM, IgG <u>Other</u> • FSH[b] • Pregnancy test (β-hCG)[c]	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

a. eGFR will be calculated using the method developed by the CKD-EPI using serum creatinine.[52]
b. FSH is collected for confirmation of postmenopausal status only.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.

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

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

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical 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 Meeting the AE Definition

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

g. 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.

h. Other situations:

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

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active

collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding,	All AEs or SAEs associated with exposure during pregnancy or breastfeeding **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 non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories, which are based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events,[64] 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 his/her assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool 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 data collection tool 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 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, 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

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

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

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

- Is not a WOCBP (see definitions below in Section 10.4.3).
- OR
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. 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 coadministered, a barrier method or other nonhormonal method of contraception must also be used if the participant is using estradiol-containing contraceptives.

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 an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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

2. Postmenopausal female:

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

if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner:

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

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

    - Oral;

    - Intravaginal;

    - Transdermal.

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

    - Oral;

    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be

evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

In addition, one of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

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

Because ritonavir may reduce the effect of estradiol-containing contraceptives when agents are coadministered, a barrier method or other non-hormonal method of contraception must also be used if the participant is using estradiol-containing contraceptives.

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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 TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and TBili for suspected 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 TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern (No Longer Applicable)

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

PF-07321332 and ritonavir are both primarily metabolized by CYP3A4. Therefore, concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to dosing of study intervention and during study treatment.

Additionally, ritonavir and PF-07321332 are inhibitors of CYP3A4. Therefore, medications highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events are not permitted during dosing of PF-07321332/ritonavir (at least 24 hours prior to the first dose of study intervention or as late as Day 1, prior to the first dose of study intervention – see below) and for 4 days after the last dose of PF-07321332/ritonavir. Ritonavir also appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase. Since ritonavir 100 mg q12h is being used to boost the exposure of PF-07321332, no additional DDI is expected other than those associated with ritonavir 100 mg q12h based on in vitro assessments. Thus, the prohibited concomitant medications and those to be used with caution are primarily based on the ritonavir label.

A nonexhaustive list of prohibited and precautionary medications is provided below. If a medication is not listed, 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.

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

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

Prohibited Medications that are Strong Inducers of CYP450 3A4[a] Due to prolonged induction of CYP450 3A4 participants must not use these medications within 28 days prior to randomization and during dosing of PF-07321332/placebo and ritonavir/placebo.		
Drug Class	**Specific Medication**	**Clinical Comments**
Anti-cancer drugs	Apalutamide	Reduced concentrations of PF-07321332/ritonavir; may result in suboptimal concentrations.
Anticonvulsants	Phenytoin, Carbamazepine, Phenobarbital	
Antimycobacterials	Rifampin	
Herbal Products	St. John's Wort	

Prohibited Medications Dependent on CYP450 3A4 for Clearance or with other Notable Interactions[a] These medications are prohibited for ***at least 24 hours prior to the first dose*** of PF-0321332/placebo and ritonavir/placebo, through 4 days after the last dose of PF-07321332/placebo and ritonavir/placebo. If a participant cannot temporarily interrupt the prohibited medication during this period, they should be considered ineligible.		
Drug Class	**Specific Medication**	**Clinical Comments**
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Risk of hypotension, syncope
Analgesics	Piroxicam, Propoxyphene, Pethidine	Analgesic concentrations may increase.
Antianginal	Ranolazine	Risk of cardiac arrhythmias
Antiarrhythmics	Dronedarone , Amiodarone, Flecainide, Propafenone, Quinidine	Risk of cardiac arrhythmias
Anti-gout	Colchicine	Ritonavir 100 mg twice daily increased colchicine AUC 296% and C_{max} 184%. Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antipsychotics	Clozapine, Lurasidone, Pimozide	Potential for increased levels of antipsychotics.
Ergot Derivatives	Dihydroergotamine, Ergotamine, Methylergonovine	Risk of acute ergot toxicity (peripheral vasospasm and ischemia of the extremities)
Lipid lowering drugs (HMG CoA Reductase Inhibitors)	Lovastatin, Simvastatin	Risk of rhabdomyolysis
PDE-5 Inhibitors for pulmonary arterial hypertension treatment	Sildenafil (Revatio) when used for pulmonary arterial hypertension	Risk of visual disturbances, Co-administration may result in visual abnormalities, hypotension, prolonged erection, and syncope.
Sedatives/ Hypnotics	oral Midazolam, Triazolam	Risk of prolonged sedation, respiratory depression, or hypnotic concentrations

a. Note: If a drug is not listed, it should not automatically be assumed it is safe to co-administer

Prohibited Medications Dependent on CYP450 3A4 for Clearance or with other Notable Interactions[a] These medications are prohibited ***from the first dose*** of PF-07321332/placebo and ritonavir/placebo, through 4 days after the last dose of PF-07321332/placebo and ritonavir/placebo. If a participant cannot temporarily interrupt the prohibited medication during this period, they should be considered ineligible.		
Drug Class	**Specific Medication**	**Clinical Comments**
Alpha 1-Adrenoreceptor Antagonist	Tamsulosin, Silodosin, Doxazosin (>2 mg daily), Terazosin (>5 mg daily),	Risk of hypotension, syncope
Analgesics Opioid Dependence Treatment	Methadone Fentanyl, Oxycodone Buprenorphine Lofexidine	Moderate to weak decreases in methadone concentrations have been observed. Analgesic concentrations may increase. Co-administration may increase concentrations of Buprenorphine and Lofexidine.
Anticancer drugs	Abemaciclib, Ceritinib, Dasatinib, Encorafenib, Ibrutinib, Ivosidenib, Neratinib, Nilotinib, Venetoclax, Vinblastine, Vincristine	Co-administration contraindicated due to potential loss of virologic response and possible resistance. 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/ antiplatelet	Rivaroxaban, Warfarin	Possible increased risk of bleeding Possible decreased warfarin effects. Closely monitor INR if co-administration with Warfarin is necessary.

Prohibited Medications Dependent on CYP450 3A4 for Clearance or with other Notable Interactions[a] These medications are prohibited ***from the first dose*** of PF-07321332/placebo and ritonavir/placebo, through 4 days after the last dose of PF-07321332/placebo and ritonavir/placebo. If a participant cannot temporarily interrupt the prohibited medication during this period, they should be considered ineligible.		
Drug Class	**Specific Medication**	**Clinical Comments**
Antidepressant	Bupropion	Monitor for an adequate clinical response to Bupropion.
	Trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of Trazodone and Ritonavir. A lower dose of Trazodone should be considered. Refer to Trazadone product label for further information.
Anti-infective (antibacterials)	Erythromycin	Co-administration may increase erythromycin concentrations.
	Clarithromycin	Co-administration may increase clarithromycin concentrations.
Antimycobacterials	Bedaquiline	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as Rifabutin should be considered.
(antifungals)	Isavuconazole Itraconazole Posaconazole Ketoconazole	Refer to Ketoconazole, Isavuconazonium Sulfate, and Itraconazole product labels for further information.
	Voriconazole	Co-administration of Ritonavir with Voriconazole may result in reduction in Voriconazole levels.
Antihistamines	Astemizole, Terfenadine	Risk of cardiac arrhythmias
Antipsychotics	Quetiapine	Co-administration may increase Quetiapine and increase risk of quetiapine-related toxicity.
	Risperidone, Perphenazine, Aripiprazole, Brexpiprazole, Cariprazine, Iloperidone, Thioridazine, Ziprasidone	Potential for increased levels of antipsychotics.
Cardiac Medications (beta blockers)	Carvedilol, Metoprolol, Timolol	Co-administration may increase concentration of Carvedilol, Metoprolol, Timolol.

Prohibited Medications Dependent on CYP450 3A4 for Clearance or with other Notable Interactions[a] These medications are prohibited ***from the first dose*** of PF-07321332/placebo and ritonavir/placebo, through 4 days after the last dose of PF-07321332/placebo and ritonavir/placebo. If a participant cannot temporarily interrupt the prohibited medication during this period, they should be considered ineligible.		
Drug Class	**Specific Medication**	**Clinical Comments**
Calcium channel blockers	Diltiazem, Verapamil, Nifedipine, amlodipine (> 5 mg daily), felodipine, nicardipine	Co-administration may increase concentrations of calcium channel blockers. The impact on the PR interval of co-administration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. A dose decrease may be needed for these drugs when co-administered with PAXLOVID.
Cardiac glycosides	Digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.
	Eplerenone	Co-administration increases eplerenone concentrations.
	Ivabradine	Co-administration increases ivabradine concentrations.
Corticosteroids (inhaled or intranasal)	Budesonide, Ciclesonide, Mometasone	Co-administration can increase concentration of Budesonide, Ciclesonide, and Mometasone and can result in adrenal insufficiency and Cushing's syndrome.
(systemic)	Betamethasone Budesonide	Co-administration can increase concentration of Betamethasone, and Budesonide and can result in adrenal insufficiency and Cushing's syndrome.
(Local injections, including intra-articular, epidural, or intra-orbital)	Betamethasone, Methylprednisolone, Triamcinolone	Co-administration can increase Betamethasone, Methylprednisolone, and Triamcinolone concentrations and can result in adrenal insufficiency and Cushing's syndrome
Endothelin receptor antagonists	Bosentan	Bosentan should be discontinued at least 36 hours prior to the initiation of ritonavir.
Hepatitis C direct acting antivirals (DAAs)	Elbasvir/Grazoprevir, Glecaprevir/Pibrentasvir	Increased Grazoprevir concentrations can result in ALT elevations. It is not recommended to co-administer ritonavir with Glecaprevir/Pibrentasvir.

Prohibited Medications Dependent on CYP450 3A4 for Clearance or with other Notable Interactions[a] These medications are prohibited ***from the first dose*** of PF-07321332/placebo and ritonavir/placebo, through 4 days after the last dose of PF-07321332/placebo and ritonavir/placebo. If a participant cannot temporarily interrupt the prohibited medication during this period, they should be considered ineligible.		
Drug Class	**Specific Medication**	**Clinical Comments**
	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 PAXLOVID or HCV drug adverse events with concomitant use.
HIV Antiretrovirals Protease Inhibitors	Lopinavir, Amprenavir, Indinavir, Nelfinavir, Atazanavir, Darunavir, Fosamprenavir, Saquinavir, Tipranavir.	Co-administration may increase HIV protease inhibitor concentrations.
	Ritonavir or cobicistat containing combination products	Risk of increased rate of adverse reactions. Appropriate doses of additional Ritonavir in combination with ritonavir-containing combination products with respect to safety and efficacy have not been established.
Integrase Inhibitors	Elvitegravir	Co-administration will increase Elvitegravir concentrations.
Hormonal contraceptive	Ethinyl Estradiol	An additional, non-hormonal method of contraception should be considered.
Lipid lowering drugs (HMG-CoA Reductase Inhibitors)	Atorvastatin (>20 mg daily), Rosuvastatin (>10 mg daily)	Risk of rhabdomyolysis
	Lomitapide	Co-administration may increase concentration of Lomitapide.

Prohibited Medications Dependent on CYP450 3A4 for Clearance or with other Notable Interactions[a] These medications are prohibited ***from the first dose*** of PF-07321332/placebo and ritonavir/placebo, through 4 days after the last dose of PF-07321332/placebo and ritonavir/placebo. If a participant cannot temporarily interrupt the prohibited medication during this period, they should be considered ineligible.		
Drug Class	**Specific Medication**	**Clinical Comments**
Hypoglycemics	Glipizide, Tolbutamide	Potentially decrease glipizide and Tolbutamide concentrations.
	Repaglinide	Potentially increase Repaglinide concentrations.
	Saxagliptin (>2.5 mg daily)	Co-administration may increase Saxagliptin concentration.
Immunosuppressants	Cyclosporine, Tacrolimus, Sirolimus, Everolimus	Co-administration may increase immunosuppressant concentrations. Therapeutic concentration monitoring is recommended for immunosuppressants.
Long-Acting Beta-Adrenoceptor Agonist	Salmeterol	The combination may result in increased concentrations of Salmeterol and increased risk of cardiovascular adverse events, including QT prolongation, palpitations and sinus tachycardia.
Neuroleptics	Pimozide	Risk of cardiac arrhythmias
Sedatives/ Hypnotics	Midazolam (parenteral), Alprazolam, Bromazepam, Brotizolam, Clonazepam, Cloniprazepam, Delorazepam, Diazepam, Etizolam, Eszopiclone, Halazepam, Lormetazepam, Nitrazepam, Nordiazpam, Quazepam, Suvorexant, Temazepam, Zaleplon, Zolpidem	Risk of prolonged sedation, respiratory depression, or hypnotic concentrations
	Clorazepate, Estazolam, Flurazepam,	Co-administration with Ritonavir may increase dose of Clorazepate, Estazolam, and Flurazepam.
	Zolpidem (> 5mg daily)	Co-administration may increase zolpidem concentration

a. Note: If a drug is not listed, it should not automatically be assumed it is safe to co-administer.

Precautionary Medications

Medications may be used with caution and require oversight by the investigator when co-administered with PF-07321332/ritonavir[a]		
Drug Class	**Specific Medication**	**Clinical Comments**
Antidepressant	Citalopram, Escitalopram, Sertraline,	No data available Co-administration may decrease Sertraline and Bupropion concentrations.
Antihypertensive Angiotensin receptor blockers:	Losartan, Valsartan	Co-administration with Ritonavir increases the level/effect of Losartan by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Ritonavir increases the level/effect of Valsartan by decreasing hepatic clearance. To be used with caution.
Antiparasitic:	Atovaquone Quinine	Co-administration with Ritonavir may decrease the concentration of Atovaquone. Co-administration with Ritonavir may decrease concentration of Quinine.
Antipsychotic:	Haloperidol	Co-administration with ritonavir increases the level/effect of Haloperidol by affecting hepatic/intestinal CYP3A4 metabolism. Haloperidol and Ritonavir both increase QTc interval. To be used with caution.
Bronchodilator:	Theophylline	Co-administration with Ritonavir may decrease Theophylline concentration.
Corticosteroids	Fluticasone	Ritonavir twice daily increases Fluticasone AUC 350-fold
HIV Antivirals Non-nucleoside reverse transcriptase inhibitors CCR5-antagonist Integrase inhibitors	Delavirdine Maraviroc Raltegravir	Co-administration may increase Ritonavir concentration. Co-administration may increase Maraviroc concentration. Raltegravir concentrations may be decreased.
Hypoglycemics	Canagliflozin	Co-administration may decrease Canagliflozin concentration.
Narcotic and Treatment for Opioid Dependence	Tramadol	Co-administration may increase concentration of Tramadol.

Medications may be used with caution and require oversight by the investigator when co-administered with PF-07321332/ritonavir[a]		
Drug Class	**Specific Medication**	**Clinical Comments**
PDE-5 Inhibitors for treatment of erectile dysfunction	Sildenafil– ED (max dose 25 mg every 48 hours) Avanafil Tadalafil (max dose 10 mg every 72 hours) Vardenafil (max dose 2.5 mg every 72 hours)	Risk of visual disturbances, hypotension, prolonged erection, and syncope
Steroids (systemic)	Dexamethasone Prednisone	Co-administration with ritonavir may increase dose of Dexamethasone and Prednisone and may increase the risk for development of systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.
Stimulant	Methamphetamine	Co-administration with Ritonavir may increase concentration of Methamphetamine.

a. Note: If a drug is not listed, it should not automatically be assumed it is safe to co-administer

10.9. Appendix 9: Signs and Symptoms Consistent With COVID-19

Table 2. Signs and Symptoms Consistent With COVID-19

Daily Sign and Symptom Collection[53]	Exclusion Criterion #2	Daily Signs and Symptom Collection	Targeted Symptoms For Analysis
Cough	X	X	X
Shortness of breath or difficulty breathing	X	X	X
Fever (documented temperature >38˚C [100.4˚F]) or subjective fever (eg, feeling feverish)	X		
Feeling feverish	X	X	X
Chills or shivering	X	X	X
Fatigue (low energy or tiredness)	X	X	X
Muscle or body aches	X	X	X
Diarrhea (loose or watery stools)	X	X	X
Nausea (feeling like you wanted to throw up)	X	X	X
Vomiting (throw up)	X	X	X
Headache	X	X	X
Sore throat	X	X	X
Stuffy or runny nose	X	X	X
Loss of smell	X	X	X
Loss of taste	X	X	X

10.10. Appendix 10: High-Risk Close Contact Behaviors

High-risk close contact is defined as any of the following exposures without the consistent appropriate use of recommended personal protective equipment (eg, face mask)[44]:

- Provided direct care for the index case
- Had close direct physical contact with the index case
- Lived with the index case
- Had close indoor contact (within 2 m), with or without direct physical contact, for at least 1 hour
- Had direct contact with infectious body fluids, including oral secretions, respiratory secretions, or stool.

10.11. Appendix 11: Risk Factors Associated With Severe COVID-19 Illness[67]

- ≥60 years of age
- BMI >25
- Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes
- Immunosuppressive disease (eg, bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
    - Has received corticosteroids equivalent to prednisone ≥20mg daily for at least 14 consecutive days within 30 days prior to study entry
    - Has received treatment with biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine), or cancer chemotherapy within 90 days prior to study entry'
    - HIV infection with CD4 cell count <200 mm^3 and a viral load less than 400 copies/mL.
- Chronic lung disease (if asthma, requires daily prescribed therapy)
- Known diagnosis of hypertension
- CVD, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass
- Type 1 or Type 2 diabetes mellitus
- CKD
- Sickle cell disease
- Neurodevelopmental disorders (eg, cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (eg, genetic or metabolic syndromes and severe congenital anomalies);
- Active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the study period;
- Medical-related technological dependence (eg, CPAP [not related to COVID-19]).

10.12. Appendix 12: Country Specific Requirements

10.12.1. Japan

A Protocol Administrative Change Letter was issued on 22 July 2021 to provide Japan country specific guidance regarding Exclusion Criterion #5 .

Exclusion Criterion #5: Known HIV infection with a viral load >400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit).

If HIV infection is known by medical interview or examination results (if any), the investigators must consult with the patient's HIV treatment specialist to confirm that the HIV RNA level has been monitored at an appropriate frequency and the HIV RNA level has been ≤400 copies/mL during the past 6 months before the screening visit in order to assess the study eligibility of that patient.

Rationale: There is a risk for patients with uncontrolled HIV to develop resistance to ritonavir which is being administered with PF-07321332. According to the HIV treatment guideline in Japan, even if there is an occasional increase in the amount of HIV RNA in the blood to about 20-500 copies/mL, the same treatment may be continued. The guideline recommends a resistance test when HIV RNA levels exceed 500 copies/mL.

10.12.2. Bulgaria

A Protocol Administrative Change Letter was issued on 26 Oct 2021 to provide Bulgaria country specific guidance regarding exclusion criteria 3 and 5 on participants with known hepatitis B or C infection (chronic or active) or poorly controlled HIV (viral load >400 copies/mL within the last 6 months).

Per guidance from Bulgarian regulatory authorities, hepatitis B and C and HIV testing must be performed for all participants being evaluated for participation in Study C4671006 to objectively confirm that participants do not have active or chronic hepatitis B or C or poorly controlled HIV infection as specified in protocol exclusion criteria 3 and 5. Required viral testing should be performed at the local laboratory and results are to be retained in participant source documents. If results for the required testing are not available within the protocol specified Screening period (24 hours prior to randomization), the participant will not be eligible to participate in the study.

Revised note on Clinical Laboratory Tests from section 1.3 (additions in bold):

- **Local testing for hepatitis B, hepatitis C and HIV is required to confirm participant eligibility per exclusion criteria 3 and 5.**

10.12.3. Ukraine

A Protocol Administrative Change Letter was issued on 22 Dec 2021 to provide Ukraine country specific guidance regarding nasal swab collection.

As per Ministry of Health of Ukraine Order # 722 dated 28-Mar-2020, requirement is made to have diagnostic tests for COVID-19 performed by a healthcare professional. The change being made in this letter is to shift from nasal swab self collection by the participants to nasal swab collection performed by a healthcare professional.

Revised note on Nasal Swab from section 1.3 (deletions in strikethrough)

- At baseline, a nasal swab will be ~~self~~ collected ~~by the participant~~ to determine RT-PCR status (+ or -); this test will not be used to determine study eligibility. ~~The sample will be collected under observation by site staff to ensure correct collection method.~~ Thereafter, nasal swabs will be ~~self~~ collected ~~by the participant~~ at about the same time each day, preferably in the morning.
- Nasal swabs will be ~~self~~ collected from Day 1 to 14 ~~including days when a study visit occurs~~ (**including at unplanned visits).

Revised first paragraph from section 8.6.4.2 (deletions in strikethrough, additions in bold):

~~The first nasal swab will be self collected by the participant under observation by site staff to ensure correct collection method. Thereafter,~~ Nasal swabs will be ~~self~~ collected by **a healthcare professional** ~~the participant~~ at about the same time each day, preferably in the morning. ~~If an in-person visit occurs on the same day as self collection of the nasal swab, the nasal swab self-collection should be done prior to the visit.~~

Additional swabs may be required at the visit on days for which an in-person visit occurs (eg, COVID-19 Signs/Symptoms Onset visit). ~~Participants~~ **A healthcare professional** should **collect** ~~conduct~~ the nasal swab ~~self-collection~~ **for Viral Load Assessment by central lab prior to any other swab** on the days described in the SoA, including those for which an in-person visit is scheduled.

It is noted that the PACL dated 14 December 2021 is not applicable in Ukraine.

10.13. Appendix 13: Glossary of Terms

Term	Definition[68-70]
Close contact	Someone who has been within 6 feet (1.8 meters) of an infected person (laboratory-confirmed or a clinically compatible illness) for a cumulative total of 15 minutes or more over a 24-hour period (for example, 3 individual 5-minute exposures for a total of 15 minutes in one day).
Contact	Exposure to a source of an infection; a person who has been exposed
Confirmed COVID-19 case	Report of person with COVID-19 and meeting confirmatory evidence.
Exposure	Having come into contact with a cause of, or possessing a characteristic that is a determinant of, a particular health problem
High-risk group	A group of persons whose risk for a particular disease, injury, or other health condition is greater than that of the rest of their community or population
Household	A group of people (two or more) living in the same residence Including, but not limited to: • Two or more people living together in a domestic residence (residential institutions, such as boarding schools, dormitories, hotels or prisons will be excluded) and • A dwelling or group of dwellings with a shared kitchen or common opening onto a shared household space
Household contact	Any person who has resided in the same household (or other closed setting) as a confirmed COVID-19 case
Incubation period	Period of time between exposure to an infection and onset of symptoms
Index case	The first case or instance of a patient coming to the attention of health authorities. For this study, the index case is the individual with the first confirmed SARS-CoV-2 infection in the household that the participant resides in. This individual is presumed to be the source case.
Isolation	The separation of a person or group of people known or reasonably believed to be infected with a communicable disease and potentially infectious from those who are not infected to prevent spread of the communicable disease. Isolation for

Term	Definition[68-70]
	public health purposes may be voluntary or compelled by federal, state, or local public health order.
Multigenerational household	Households that consist of more than 2 generations living under the same roof. Many researchers also include households with a grandparent and at least one other generation.
Quarantine	The separation of a person or group of people reasonably believed to have been exposed to a communicable disease but not yet symptomatic from others who have not been so exposed to prevent the possible spread of the communicable disease. Quarantine may be voluntary or compelled by federal, state, or local public health order.
Secondary attack rate	A measure of the frequency of new cases of a disease among the contacts of known patients
Source Case	The case or instance of a patient responsible for transmitting infection to others; the instance of a patient who gives rise to an outbreak or epidemic

10.14. Appendix 14: Abbreviations

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

Abbreviation	Term
3CL	3C-like protein
6MP	mercaptopurine
Abs	absolute
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BID	twice a day
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CCR5	chemokine receptor type 5
CD4	cluster of differentiation 4
CDC	United States Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHW	Cui, Hung, and Wang
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
CT	clinical trial
C_{trough}	predose concentration
CVD	cardiovascular disease

Abbreviation	Term
CYP	cytochrome P450
DAA	direct acting antivirals
DAIDS	Division of AIDS
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
dNHBE	differentiated normal human bronchial epithelial cells
DU	dispensable unit
EC	ethics committee
EC_{90}	concentration required for 90% effect
ECC	emergency contact card
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
eCRF	electronic case report form
ED	erectile dysfunction
EDB	exposure during breastfeeding
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions 3-Levels
EQ-5D-5L	EuroQol-5 Dimensions 5-Levels
ET	early termination
EU	European Union
EUA	Emergency Use Authorization
EudraCT	European Clinical Trials Database
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
f_u	fraction of unbound drug in serum or plasma
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
H_a	alternative hypothesis
HCoV	human coronavirus
HCP	health care professional; health care provider
HCV	hepatitis C virus
HDPE	high-density polyethylene

Abbreviation	Term
HF	heart failure
HIV	human immunodeficiency virus
H_0	Null hypothesis
HR	heart rate
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
HTA	health technologies assessment
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
IWR	interactive Web-based response
LDH	lactate dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
MAD	multiple ascending dose
mITT	modified intent-to-treat
MMRM	mixed-effect model repeated measure
MRC-5	human lung epithelial cells-5
msec	millisecond
NA	not applicable
NCT	national clinical trial
NHP	non-human primate
NIH	National Institutes of Health
NIMP	noninvestigational medicinal product
NP	nasopharyngeal
PACL	protocol administrative change letter
PCI	percutaneous coronary intervention
PDE-5	phosphodiesterase
PK	pharmacokinetic(s)
PP	Per-protocol
PRO	patient-reported outcome
PT	prothrombin time

Abbreviation	Term
PVC	premature ventricular contraction
q12h	every 12 hours
QSP	Quantitative Systems Pharmacology
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT
QTcF	corrected QT using Fridericia's formula
QTL	quality tolerance limit
RBC	red blood cell
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
RT-qPCR	real-time quantitative polymerase chain reaction
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SoA	schedule of activities
SoC	standard of care
SOC	System Organ Class
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
T4	thyroxine
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information; United States Package Insert
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-GH	Work Productivity and Activity Impairment Questionnaire-General Health

10.15. Appendix 14: Protocol Amendment History

Amendment 1 (20 August 2021)
The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC). The protocol amendment summary of changes tables for past amendment(s) can be found below:

Overall Rationale for the Amendment 1:
The protocol was amended to modify the eligibility criteria for the study to exclude Rapid Antigen Test positive participants, modify the primary analysis set, and provide clearer guidance for assessment of participants who develop symptomatic SARS-CoV-2 infection.

Section # and Name	Description of Change	Brief Rationale
3. Objectives, Endpoints, and Estimands 9. Statistical Considerations	Primary analysis set limited to participants who have a negative RT-PCR result at baseline. Primary and secondary estimand/endpoints adapted to include adults who have a negative RT-PCR result at baseline, as applicable. Additional detail provided in description of primary and key secondary analyses including intercurrent event.	By excluding participants with a positive RT-PCR result at baseline from the primary analysis set, this analysis more accurately reflects postexposure prophylaxis. Addition of intercurrent events provides greater clarity to the analysis of primary and key secondary endpoints.
1. Protocol Summary 4.1 Overall Design 9.5. Sample Size Determination	Increased sample size	Increased sample size accounts for participants who have a negative screening antigen test, but who subsequently have a positive RT-PCR result at baseline.
4.1. Overall Design	Removal of stratification variable based on rapid antigen test.	Removal of this stratum accounts for exclusion of participants who have a positive screening antigen test.
1. Protocol Summary 4.1. Overall Design 10.1.5.1. Data Monitoring Committee	Enrollment pause for unblinded E-DMC safety data review of sentinel cohort E-DMC meeting frequency specified.	Enrollment pause allows time for E-DMC review of sentinel cohort safety data prior to further enrollment. E-DMC meeting frequency provides greater clarity in the protocol.

Section # and Name	Description of Change	Brief Rationale
1. Protocol Summary 4.1. Overall Design 10.1.5.1. Data Monitoring Committee 9.4. Interim Analyses	Futility assessment incorporated into interim analysis. More details on interim analysis including stopping boundaries and discontinuation of treatment groups	Futility assessment provides for the E-DMC to discontinue one or both active treatment groups.
1.3 Schedule of Activities 4.2. Overall Design 8.1.2. Daily Signs and Symptoms of COVID-19 8.1.3. COVID-19 Related Medical Visit Details 8.2.4. Vital Signs	Addition of COVID-19 Signs/ Symptoms Onset visit, including triggers for the visit and assessments to be performed.	Addition of this visit provides guidance for assessment of participants who develop COVID-19 symptoms.
5.1. Inclusion Criteria	Participants must have a negative screening SARS-CoV-2 rapid antigen test to be included in the study.	Exclusion of participants with a positive screening antigen test will reduce enrollment of participants with positive baseline RT-PCR results.
10.9. Signs and Symptoms Attributable to COVID-19	Addition of loss of taste and loss of smell to exclusionary symptoms and to symptoms that will be assessed in efficacy analyses.	Loss of taste/smell is a frequent first symptom associated with SARS-CoV-2 infection.
5.2. Exclusion Criteria	Exclusion of participants with history of positive test for anti-SARS-CoV-2 antibody.	Exclusion of participants with history of positive SARS-CoV-2 antibody test will reduce factors that may obscure treatment effect.
5.2. Exclusion Criteria	Addition of approved, authorized or investigational anti-SARS-CoV-2 treatments to the list of prohibited medications for study entry.	Increases focus of eligibility on postexposure prophylaxis.
9.1.2. Multiplicity Adjustment	Clarification that if one of the PF-07321332/ritonavir groups is discontinued, sequential testing	Increase clarity on multiplicity adjustment if one of the

Section # and Name	Description of Change	Brief Rationale
	will be performed in the remaining PF-07321332/ritonavir group in the order of the primary endpoint and key secondary endpoint.	PF-07321332/ritonavir groups is discontinued.
10.12.2. Japan	Japan country-specific requirement for consultation on HIV RNA monitoring.	Inclusion of this consultation incorporates country-specific changes to the global protocol.
6.8 Concomitant Therapy	Clarification that participants who develop COVID-19 may receive SoC therapy.	Clarification ensures appropriate treatment of participants.
1.3. Schedule of Activities 8.2.6. Clinical Safety Laboratory Assessments	Investigators are instructed to contact the Medical Monitor if baseline lab results meet exclusion criteria.	Enables investigator to review disposition and follow-up with the Medical Monitor for participants with baseline laboratory abnormalities.
1.3. Schedule of Activities	Day 14 and Day 38 will be in-person visits for all participants.	Provides for collection of blood for serology testing for all participants, but maintains reflex testing for safety laboratory tests.
	Collection of blood samples for SARS-CoV-2 serology on Day 14 and Day 38 for all participants.	Increases understanding of exposure and immune response to SARS-CoV-2 infection.
1.3. Schedule of Activities 8.6.5. Assessments for Other Respiratory Pathogens	Additional testing for respiratory pathogens at central laboratory for protocol-required nasal swabs and additional local testing per local standard of care.	Allows identification of other respiratory pathogens besides SARS-CoV-2
1.3. Schedule of Activities 8.6 Biomarkers 8.6.4.2. Viral Load Assessments	Removal of NP swabs. Instruction that first nasal swab is to be self collected by participant under observation of site staff.	NP swabs removed to use a consistent swab source (nasal). First nasal swab will be self collected by participant under observation of site staff to ensure correct collection method.
8.6.4.2. Viral Load Assessments	SARS-CoV-2 positive nasal swab samples will undergo additional testing.	Increases understanding of SARS-CoV-2 kinetics in study participants.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Updates to description of visit conditions in footnotes.	Increases clarity for study conduct.
1.3 Schedule of Activities	Added footnote describing the study intervention dispensation.	Increases clarity for study conduct.
6.3.2. Blinding of the Sponsor	Description of sponsor blinding and unblinded team.	Increases clarity for study conduct.
6.2. Preparation, Handling, Storage, and Accountability	Guidance added regarding shipping study intervention by courier and temperature monitoring for ground transportation.	Increases clarity for study conduct.
1.3. Schedule of Activities	Allowance for investigators to change a telemedicine visit to in-person at their discretion.	Increases clarity for study conduct.
8.2.2. Height and Weight	Height may be self reported.	Consistency with other C467 Phase 2/3 studies.
Protocol Title 1. Protocol Summary 2. Introduction 3. Objectives, Endpoints, and Estimands	Index cases described as individuals with "symptomatic COVID-19".	Document clarity and consistency
8. Study Assessments and Procedures	Correct total blood sampling volume.	Document clarity and consistency.
10.4.3. Woman of Childbearing Potential	FSH is used to confirm postmenopausal state in women under 50 years of age.	Document clarity and consistency.
Title Page	Phase 3 was updated to Phase 2/3.	Document clarity and consistency.
Throughout	Editorial changes and correction of typographical errors.	Document clarity and consistency.

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