AN INTERVENTIONAL EFFICACY AND SAFETY, PHASE 2/3, DOUBLE-BLIND, 2-ARM STUDY TO INVESTIGATE ORALLY ADMINISTERED PF-07321332/RITONAVIR COMPARED WITH PLACEBO IN NONHOSPITALIZED SYMPTOMATIC ADULT PARTICIPANTS WITH COVID-19 WHO ARE AT INCREASED RISK OF PROGRESSING TO SEVERE ILLNESS

Study Intervention Number:	PF-07321332
Study Intervention Name:	N/A
US IND Number:	153517
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Protocol Number:	C4671005
Phase:	2/3

Brief Title: *A Phase 2/3 Efficacy and Safety Study of PF-07321332/Ritonavir in Nonhospitalized High Risk Adult Participants With COVID-19*

Document History

Document	Version Date
Amendment 4	20 November 2021
Amendment 3	26 October 2021
Amendment 2	02 August 2021
Amendment 1	02 July 2021
Original protocol	18 June 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.

Protocol Amendment Summary of Changes Table

Amendment 4 (20 November 2021)

Overall Rationale for the Amendment: To remove the second interim analysis (70% interim analysis that was added under Amendment 3) from the protocol because the objective of the planned 45% interim analysis was met.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	• Second interim analysis at 70% has been removed, and sample size updated to lower it from 3100 to approximately 3000 participants due to removal of second interim analysis. • Study enrollment will be stopped after approximately 1717 participants are available for the primary analysis.	The 70% interim analysis has been removed because the planned interim analysis objective was achieved.
Section 2.3.3 Overall Benefit/Risk Conclusion	Text updated to clarify that the 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 and futility at the time of the interim analysis.	To be consistent with the rest of the document.
Section 4.1 Overall Design	• Sample size updated to lower it from 3100 to approximately 3000 participants due to	To provide a more comprehensive description of the overall study design and specifically to reduce the sample size

Section # and Name	Description of Change	Brief Rationale
	removal of second interim analysis. • Removed second interim analysis.	in response to the interim analysis outcome.
Section 9 Statistical Considerations	• 9.3.2 Primary Endpoint(s)/Estimand(s) Analysis: updated to remove primary analysis being conducted for 2 planned interim analyses. • 9.4. Interim Analyses: Second interim analysis removed. The 45% interim analysis boundary was updated as a result, and a sentence added regarding boundaries at end of trial. • 9.5 Sample Size Determination: text updated due to removal of second interim analysis: Study enrollment will be stopped after approximately 1717 participants are available for the primary analysis. • Total sample size changed from 3100 to 3000 participants.	The second interim analysis has been removed and as a result the sample size has been modified back to the number of participants in the original design.
Section 10 Supporting documentation and Operational considerations	Second interim analysis removed.	The second interim analysis has been removed from the Data Monitoring Committee description under Committee Structure.
Throughout the protocol	Typographical errors were corrected and minor edits were made.	For clarification and to ensure consistency.

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1. PROTOCOL SUMMARY

1.1. Synopsis

An Interventional Efficacy And Safety, Phase 2/3, Double-Blind, 2-Arm Study To Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo In Nonhospitalized Symptomatic Adult Participants With Covid-19 Who Are At Increased Risk Of Progressing To Severe Illness.

Brief Title: A Phase 2/3 Efficacy and Safety Study of PF-07321332/Ritonavir in Nonhospitalized High Risk Adult Participants With COVID-19

Rationale

The purpose of this study is to evaluate the efficacy and safety of PF-07321332/ritonavir for the treatment of nonhospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness.

Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.
Secondary:	**Secondary:**	**Secondary:**
• To describe the safety and tolerability of PF-07321332/ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	Not applicable.
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28	The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe

Objectives	Endpoints	Estimands
		disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomized treatment.
• To compare PF-07321332/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28. • Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28. • Time (days) to sustained resolution of all targeted signs/symptoms through Day 28. • Duration of each targeted COVID-19 sign/symptom. • Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28. • Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	The absolute difference in median time to sustained alleviation or resolution of symptoms for all nonhospitalized adult patients with COVID-19 who are at increased risk of progression to severe disease. This will be estimated irrespective of adherence to randomized treatment.
• To compare PF-07321332/ritonavir to placebo for all-cause mortality in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with death (all cause) through Week 24.	• Not applicable.
• To determine the PK of PF-07321332 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable
• To describe the viral load in nasal samples over time in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.
• To compare PF-07321332/ritonavir to placebo for COVID-19-related medical visits in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of COVID-19 related medical visits through Day 28.	• Not applicable
• To compare PF-07321332/ritonavir to placebo for COVID-19-related hospitalizations in	• Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.	• Not applicable.

Objectives	Endpoints	Estimands
nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.		

Overall Design

Brief Summary

This Phase 2/3, randomized, double-blind, placebo-controlled study in nonhospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo. Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection will be randomized (1:1) to receive PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Randomization will be stratified by geographic region and whether participants have received/are expected to receive COVID-19 therapeutic mAb treatment (yes/no) based on the site investigator's assessment at the time of randomization.

Enrollment of participants who have received/are expected to receive COVID-19 therapeutic mAb treatment is expected to be approximately 20% and will be limited to approximately 25% of participants. Enrollment of participants that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25% and will be limited to a total of approximately 1000 participants.

Number of Participants

Approximately 3000 participants will be randomly assigned to study intervention.

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

Participants will be screened within 48 hours of randomization. Eligible participants will receive PF-07321332 plus ritonavir or placebo orally q12h for 5 days. The total study duration is up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

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, as specified in the E-DMC Charter. In addition to up to weekly reviews of safety, the E-DMC will review the following:

- Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 60 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.

- Proof-of-concept assessment: The E-DMC will review viral load data when approximately 200 participants in the primary analysis set with evaluable data complete the Day 5 assessments. Enrollment will not be paused during review of these data but may be paused or stopped following E-DMC review.

- Interim analysis: A planned interim analysis for efficacy and futility will be done after approximately 45% of participants in the mITT analysis set complete the Day 28 assessments (ie, 28 days after randomization).

Statistical Methods

The cumulative proportion of participants hospitalized for the treatment of COVID-19 or dying during the first 28 days of the study will be estimated for each treatment group using the Kaplan-Meier method to take account of losses to follow-up and summarized graphically for each treatment group. The estimand is then the difference of the proportions in the 2 groups and its 95% CI will be presented as well as the associated Wald test. For the 95% CI, the corresponding estimate of the standard error is computed using Greenwood's formula.[1] The Greenwood's formula to estimate the variance of the difference of proportions at Day 28 is [$Var(S_{PF}(28)) + Var(S_{Placebo}(28))$]. Instead of dealing with $S(t_i)$ the log-log approach to CI will be used. The 95% CI will be computed for the estimate of $L(t)= \log(-\log(S(t)))$, the log hazard function.

The above primary analysis will also be conducted for the planned interim analysis. Two-sided 95% CI (adjusted for the planned interim analysis) and associated p-value for the null hypothesis of no difference between treatment groups will be presented. Significance level will be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall significance level is set at 5% (2 sided).

The estimate of required sample size is based on data from the BLAZE-1 Phase 2/3 trial among participants with mild to moderate COVID-19 who were at high risk for progressing to severe COVID-19 and/or hospitalization at enrollment.[2] During the 29-day period following enrollment, the proportion of placebo-treated participants with a COVID-19-related hospitalization/emergency department visit was 7% in the Phase 3 portion of the trial.[3]

This study is designed to have 90% statistical power to show a difference of 3.5% in the proportion of participants hospitalized/dying that did not receive COVID-19 therapeutic mAb between the treatment arms (PF-07321332/ritonavir versus placebo), using a 2-sided Type I error rate of 5%. Based on the above study[2], the proportion of hospitalization/death in the placebo arm is assumed to be 7%.

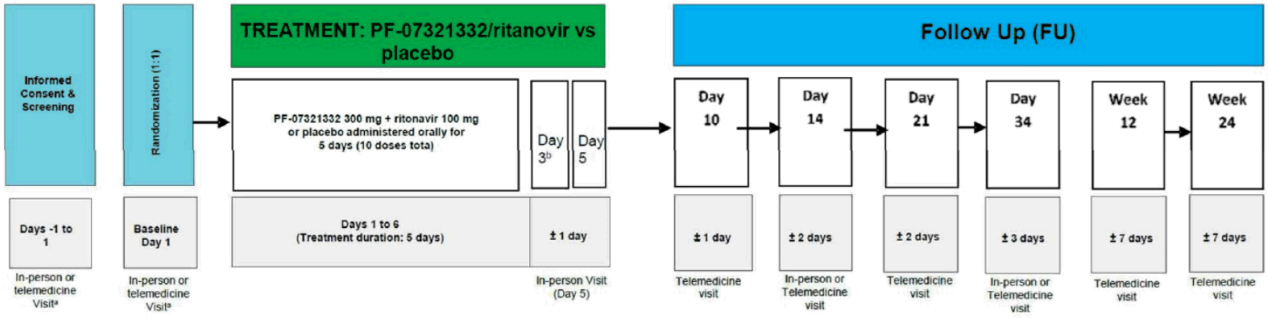
For a 2-sample proportion test, the sample size needed to detect this difference with 90% power at a 2-sided significance level of 5% was determined to be 1717 randomized participants.

Enrollment of participants that have received/are expected to received COVID-19 therapeutic mAb treatment is expected to be approximately 20% of participants and will be limited to approximately 25% of participants. Enrollment of participants that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25%, and will be limited to a total of approximately 1000 participants. Assuming a 5% dropout rate, the total sample size for this study will be approximately 3000 participants.

Study enrollment will be stopped after approximately 1717 participants are available for the primary analysis.

The primary estimand is the difference in proportions of patients experiencing COVID-19 related hospitalization or death from any cause through Day 28 in nonhospitalized adult participants with COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.

1.2. Schema



a. The baseline and screening visits may be a combination of in-person and telemedicine visits.
b. The Day 3 visit must be conducted in-person for the first 60 participants (sentinel cohort) and thereafter only if a PK sample (not using Tasso) is collected by an HCP or if ECG is required.

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 12.	**Screening**	**Baseline (Day 1)**	**Day 3**	**Day 5**	**Day 10**	**Day 14**	**Day 21**	**Day 34**	**LT F/U**		**ET (prior to Day 34)**	**Notes**
									Week 12	**Week 24**		
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	
ELIGIBILITY												
Informed consent	X											• See Section 10.1.3.
Verify inclusion/exclusion criteria	X											• See Section 5.1 and Section 5.2.
Demographics and medical history	X											• See Section 8.2.1.
COVID-19 risk factor assessment	X											• See Appendix 9.
PHYSICAL EXAMINATION & VITAL SIGNS												
Targeted physical examination	X	X		X		[X]		[X]			[X]	• Targeted physical examinations will be completed at all in-person visits and on Days 14 and 34 and ET (prior to Day 34) if conducted in person. In the event that an in-person visit is not feasible at the investigational site, targeted physical examinations may be performed by a licensed HCP at an alternate site approved by the investigator (eg, the participant's home) when feasible. • AEs should be assessed by means of a telemedicine visit if not feasible via 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. • See Section 8.2.3 and Section 8.2.4.
Vital signs	X	X	[X]	X		[X]		[X]			[X]	

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	Screening	Baseline (Day 1)	Day 3	Day 5	Day 10	Day 14	Day 21	Day 34	LT F/U		ET (prior to Day 34)	Notes
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Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	
Weight, height	X											• Height may be self reported. • See Section 8.2.2.
ECG		X	X	X		X						• Will be assessed for the first 60 participants (sentinel cohort). Further ECG monitoring may occur pursuant to E-DMC or FDA recommendation after the sentinel cohort safety review (Section 10.1.5.1). • See Section 8.2.5.
LABORATORY												
Hematology		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 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. • Laboratory tests at Days 14 and 34 are required only if clinically relevant abnormal laboratory values were present from a sample drawn at the previous study visit when laboratory assessments were performed.
Blood chemistry		X		X		[X]		[X]			[X]	
Other laboratory assessments		X		X		[X]		[X]			[X]	

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	Screening	Baseline (Day 1)	Day 3	Day 5	Day 10	Day 14	Day 21	Day 34	LT F/U		ET (prior to Day 34)	Notes
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Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	
												• Abnormal laboratory values related to AEs should be followed until resolution. See Section 8.2.6 and Appendix 2.
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 34 or ET visit. • See Section 8.2.7.
FSH	X											• FSH is to be performed 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 age 50 to 60 years with no menses for 12 months do not need FSH testing to be performed to confirm postmenopausal status. • 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.
Rapid antigen testing	X											• Only required if a participant does not have results of a positive SARS-CoV-2 test that was obtained within 5 days prior to randomization. • Refer to Section 5.1.
Viral load assessment		X	X	X	X	X						• At baseline, an NP swab will be collected by the investigational site staff to confirm SARS-CoV-2 infection by RT-PCR. This test will not be used to determine study eligibility. Subsequent NP or nasal swabs will be collected on Days 1, 3, 5, 10, and 14. o NP swabs will be collected by an HCP during an in-person visit. Otherwise, a nasal

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	Screening	Baseline (Day 1)	Day 3	Day 5	Day 10	Day 14	Day 21	Day 34	LT F/U		ET (prior to Day 34)	Notes
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Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	
												swab will be self collected by the participant. • See Section 8.6.4.
CCI [redacted]		[redacted]		[redacted]		[redacted]						[redacted]
CCI [redacted]		[redacted]		[redacted]		[redacted]						[redacted]
CCI [redacted]		[redacted]		[redacted]		[redacted]						[redacted]
PK												
PK sample (PF-07321332)		X		X								• On Day 1, one blood sample for PK will be collected 30 to 90 minutes postdose if feasible for the participant to remain at the site. • On Day 5, one blood sample for PK will be collected. The preferred time of sample collection is predose up to 2 hours before study intervention administration; if a predose sample collection is not possible, collect this sample at anytime during the visit, even after study intervention has been administered. • Refer to Section 8.4.
Optional PK sampling ([PF-07321332] collected via home health, site visit, or self collected using Tasso; in a subset of participants, if feasible)			X									• PK sample(s) will be collected either during in-person visit (a single blood sample collected at any time on either Days 2, 3, or 4) or self-collected by Tasso microsampling device (selected sites) at the following timepoints: o Day 2 before the evening dose, o 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

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	Screening	Baseline (Day 1)	Day 3	Day 5	Day 10	Day 14	Day 21	Day 34	LT F/U		ET (prior to Day 34)	Notes
									Week 12	Week 24		
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	
												(the last sample should be collected before the evening dose). • Refer to Section 8.4
RANDOMIZATION		X										
STUDY INTERVENTION												
Study intervention administration		Day 1 through Day 5 (10 doses total)										• If 1 dose was administered on Day 1, study intervention administration should end on Day 6. • See Section 6.1.
STUDY PROCEDURES & ASSESSMENTS												
Collect/update secondary contacts		X		X	X	X	X	X	X			• The investigator will capture contact information for at least 2 individuals who the site can contact if the participant is unable to be reached after multiple attempts. • At baseline, the investigator will also request contact information for any household members who may be eligible to participate in Study C4671006 as applicable.
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										
Participant-completed study diary (COVID-19 signs and symptoms and global impression questions)		Every day from Day 1 through Day 28										• See Section 8.1.1 and Section 8.1.5.1. • Global impression questions will be answered every day from Day 1 through Day 28 after COVID-19 signs and symptom diary is completed. • These additional questions will only be assessed in participants who enroll after the sentinel cohort (ie, the first 60 participants) as available.
WPAI				X		X			X	X		• Will only be assessed in participants who enroll after the sentinel cohort (ie, the first 60 participants) as available. • See Section 8.1.5.2.

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	Screening	Baseline (Day 1)	Day 3	Day 5	Day 10	Day 14	Day 21	Day 34	LT F/U		ET (prior to Day 34)	Notes
									Week 12	Week 24		
Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	
EQ-5D-5L		X		X		X		X	X	X		• Will only be assessed in participants who enroll after the sentinel cohort (ie, the first 60 participants) as available. • See Section 8.1.5.3.
Staff review of study diary		X	X	X	X	X	X	X			X	• See Section 8.1.1.
Participant-completed study intervention log		Day 1 through Day 5/6										• Study intervention log should be completed daily on Days 1 through Day 6 if only 1 dose was administered on Day 1. • See Section 6.4.
Record COVID-19-related medical visits				X	X	X	X	X				• COVID-19-related medical visits a participant has attended since the last assessment will be collected. • See Section 8.1.2.
Retrieval of unused study intervention and empty study intervention containers				X		[X]		[X]			X	• If the Day 5 visit is conducted prior to last dose of study intervention, the study intervention log, 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			X [if needed]	• Study intervention accountability is only performed at the Day 14 visit if the participant administered treatment after the Day 5 visit was conducted. If the Day 14 visit is not an in-person visit, study intervention accountability will then be performed during the Day 34 visit. • See Section 6.4.
Contraception check		X		X	X	X	X	X			X	• See Section 5.3.1.
Vital status check									X	X	X	
Long-term follow-up telemedicine interview									X	X		• Staff will ask participants if they are experiencing COVID-19 signs and symptoms and conduct a vital status check.
CONCOMITANT TREATMENT(S)												
Prior/concomitant medications	X	X		X	X	X	X	X			X	• All prescription and over-the-counter medications including vaccines taken by the participant within

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Visit Window	**Day -1 to Day 1**	**0 days**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±3 days**	**±7 days**	**±7 days**	**±5 days**	
												30 days before study entry (considered prior treatment) will be recorded. • Concomitant therapies will be collected through the Day 34 visit. • Refer to Section 6.8.
Adjunctive therapeutic procedures	X	X		X	X	X	X	X			X	• Will be collected through the Day 34 visit.
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 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 study intervention.
- **Day 1** is the start of dosing.
- **For Study Intervention Administration**: Participants will receive study intervention for 5 days (10 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, 9) will be self-administered outside the study clinic (eg, at home).
- **Screening**, **Baseline**, and **Day 5** visits will be conducted in-person (at the investigational site approved by the investigator or a remote location, including a participant's home).
- **Day 3** must be conducted in-person for the first 60 participants (sentinel cohort) and thereafter only if a PK sample (not using Tasso) is collected by an HCP or if ECG is required.
- **Day 3** and **Day 5** visits should be conducted on separate calendar days.
- **Day 10, Day 21, Week 12** and **Week 24** visits will be conducted by telemedicine system. Telemedicine visits may be converted to an in-person visit at the discretion of the investigator.
- **Day 14** visit must be conducted in-person for the first 60 participants (sentinel cohort). Thereafter the visit may be conducted in-person or by telemedicine. After the sentinel cohort the visit must be conducted in person only if ECG is required.
- **Day 34** visit will be conducted in-person or by telemedicine system.
- **Early Termination prior to Day 34** visit will be conducted in-person or by telemedicine system.

2. INTRODUCTION

PF-07321332, a potent and selective SARS-CoV-2 3CL protease inhibitor, is being investigated as an oral antiviral treatment of COVID-19.

2.1. Study Rationale

The purpose of this study is to evaluate the efficacy and safety of PF-07321332/ritonavir for the treatment of nonhospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness.

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[4] on 30 January 2020 and further characterized the disease outbreak as a pandemic on 11 March 2020.[5] As of June 2021, at least 171,776,210 cases have been confirmed worldwide, and at least 3,693,623 deaths have occurred.[6]

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,[7] patients who are hospitalized with COVID-19 may have significant morbidity and mortality,[8,9] 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.[10-13] Moreover, other comorbidities, such as hypertension, obesity, and diabetes, as well as older age and male sex increase the risk for worse outcomes.[14]

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.[15-17] The FDA has approved IV remdesivir,[18] 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[19] across the COVID-19 spectrum or has shown modest effects.[20,21] Favipiravir is currently under investigation for its activity against SARS-CoV-2 due to its broad-spectrum activity against various RNA viruses[22,23] and has been approved in India and Russia to treat mild to moderate COVID-19.[24] 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.[22]

Three IV-administered mAb based regimens have received EUA for treatment of COVID-19 in the outpatient setting for high risk persons on the basis of observed reductions in hospitalizations and deaths in placebo-controlled randomized controlled trials.[3,25,26]

Eligibility for mAbs is limited to persons meeting EUA-defined criteria of being at high risk for progression to severe COVID-19 or hospitalization, may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction and require patients be monitored during administration and for at least 1 hour after infusion is complete. In addition, as the mAb based regimens primarily target the variable spike protein, there is ongoing risk that the continued emergence of SARS-CoV-2 variants will negatively impact the efficacy of mAb based regimens.

There is thus a high unmet need for antiviral agents that could be used for the treatment of nonhospitalized persons with COVID-19. Such agents, particularly those that target highly conserved viral targets, don't require administration in a healthcare setting, and with a risk/benefit profile supportive of administration to a broad patient population will significantly add to the treatment armamentarium for COVID-19.

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).[27] 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 in patients with COVID-19.

In this study, PF-07321332 will be coadministered with ritonavir. Ritonavir is a strong CYP3A4 inhibitor, and is being coadministered with PF-07321332 to achieve exposures sufficient to suppress viral replication through the entire dosing interval (ie, $C_{trough}>EC_{90}$). Ritonavir is not expected to have any antiviral activity against the SARS-CoV-2 virus.

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.[28]

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 indicate that 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 that 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.

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 ritonavir is the USPI 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 HIV-positive patients who are HIV-positive at 600 mg BID.	Lower dose of 100 mg twice daily is used in this study. There will be close observation of AEs. In addition to ongoing review of AEs by the sponsor, an E-DMC will review safety data as described in Section 10.1.5.1. Taking study intervention with food may improve tolerability.
Neurological disturbances (eg, paresthesia, including oral paresthesia, dysgeusia and dizziness)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs. In addition to ongoing review of AEs by the sponsor, an E-DMC will review safety data as described in Section 10.1.5.1.
Rash (most commonly reported as erythematous and maculopapular, followed by pruritic)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs and monitoring through targeted physical exams. If needed therapeutic interventions per SoC may be provided.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Fatigue/Asthenia	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs. Fatigue (low energy or tiredness) will be assessed through collection of daily signs and symptoms and will also be assessed through targeted physical examinations when performed during the study visits.

2.3.2. Benefit Assessment

PF-07321332 has been shown to have SARS-CoV-2 antiviral activity in vitro and is intended to reduce virus titers, thereby reducing the duration and severity of symptoms and the risk of mortality in SARS-CoV-2 infected patients. On this basis, the potential benefit to individual study participants who receive the study intervention may include a shorter time to clinical recovery, prevention of hospitalization, and a lower probability of progressing to more severe illness or death. The potential benefit of the study is that it may provide a new treatment option for nonhospitalized patients with COVID-19 who are at increased risk for progression to severe disease and hospitalization. In the context of the global pandemic public health emergency, this treatment could play an important role in alleviating current pressures on health care systems globally.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the current COVID-19 global pandemic and the high burden of both mortality and morbidity and the potential for future epidemic outbreaks, the lack of readily available outpatient treatment options, and the measures taken to minimize risk to participants in this study, the potential risks identified in association with PF-07321332 are justified by the anticipated benefits that may be afforded to participants with COVID-19. 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 and futility at the time of the planned interim analysis according to the E-DMC Charter.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease ,who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.
Secondary:	**Secondary:**	**Secondary:**
• To describe the safety and tolerability of PF-07321332/ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at increased	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	Not applicable.

Objectives	Endpoints	Estimands
risk of progression to severe disease.		
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28	The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomized treatment.
• To compare PF-07321332/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28. • Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28. • Time (days) to sustained resolution of all targeted signs/symptoms through Day 28. • Duration of each targeted COVID-19 sign/symptom. • Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28. • Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	The absolute difference in median time to sustained alleviation or resolution of symptoms for all non-hospitalized adult patients with COVID-19 who are at increased risk of progression to severe disease. This will be estimated irrespective of adherence to randomized treatment.
• To compare PF-07321332/ritonavir to placebo for all-cause mortality in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with death (all cause) through Week 24.	• Not applicable.
• To determine the PK of PF-07321332 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable.
• To describe the viral load in nasal samples over time in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.

Objectives	Endpoints	Estimands
• To compare PF-07321332/ritonavir to placebo for COVID-19-related medical visits in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of COVID-19 related medical visits through Day 28.	• Not applicable.
• To compare PF-07321332/ritonavir to placebo for COVID-19-related hospitalizations in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.	• Not applicable.

4. STUDY DESIGN

4.1. Overall Design

This Phase 2/3, randomized, double-blind, placebo-controlled study in approximately 3000 symptomatic participants with COVID-19 who are nonhospitalized will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo. Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection will be randomized (1:1) to receive PF-07321332 and ritonavir or placebo orally q12h for 5 days (10 doses total). Randomization will be stratified by geographic region and by whether participants have received/are expected to receive treatment with COVID-19 therapeutic mAbs based on the site investigator's assessment at time of randomization. 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.

Enrollment of participants who have received/are expected to receive COVID-19 therapeutic mAb treatment is expected to be approximately 20% and will be limited to approximately 25% of participants. Enrollment of participants that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25% and will be limited to a total of approximately 1000 participants.

The total study duration is up to 24 weeks and includes a screening period of no more than 48 hours, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow up at Weeks 12 and 24.

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

- Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 60 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.

- Proof-of-concept assessment: The E-DMC will review viral load data when approximately 200 participants in the primary analysis set with evaluable data complete the Day 5 assessments. Enrollment will not be paused during review of these data but may be paused or stopped following E-DMC review.

- Interim analysis: A planned interim analysis for efficacy and futility with a sample size re-estimation will be done after approximately 45% of participants in the mITT analysis set complete the Day 28 assessments (ie, 28 days after randomization).

Subsequent to the planned interim analysis, there will be 2 analyses for reporting the results of this study. The primary analysis will be performed after all participants have completed the Day 34 visit. The follow-up analysis will be performed after all participants have completed the Week 24 visit.

4.2. Scientific Rationale for Study Design

This study evaluates safety and the potential effect of an investigational agent on reducing COVID-19 related hospitalizations and death (all cause), and, as a secondary endpoint, the duration and severity of COVID-19-associated symptoms because participants are symptomatic upon entry to this study. Previous studies with mAbs directed against the SARS-CoV-2 spike (S) protein that have received an EUA from the US FDA showed efficacy in reducing hospitalizations and/or death in high-risk participants, as well as reducing SARS CoV-2 shedding on NP swabs and time to symptom resolution.[3,25,26] Efficacy assessments (including participant reported COVID-19 symptoms and severity, COVID-19-related medical visits, and vital status) will be collected through Day 28. The symptom endpoint includes those recommended by FDA and relies on targeted symptoms that have been associated with COVID-19, and which are expected to be dynamic and improve with effective anti-SARS-CoV-2 therapy. NP/nasal swabs will be collected at specified timepoints to assess viral load over time.

This study uses a randomized, double-blind, placebo-controlled design, which is a well-accepted approach for evaluating efficacy in a clinical research setting. Placebo was selected as the comparator because there is no- globally approved SoC treatment for this patient population as of June 2021. Participants in either treatment group may receive SoC therapy so long as it is not prohibited under Section 5.1 or Appendix 8. Because the NIH COVID-19 Treatment Guidelines panel[29] recommends use of the available EUA mAb therapies for the treatment of outpatients with mild to moderate COVID-19 who are high risk of clinical

progression, participants enrolled in the US (and other countries, depending on availability), may receive COVID-19 therapeutic mAb as SoC treatment. Randomization will be stratified at entry based by geographic region and by whether participants have received/are expected to receive a COVID-19 therapeutic mAb treatment (yes/no).

Because of limited in-human dosing before this Phase 2/3 study, an early safety analysis (with enrollment pause) will be conducted by the E-DMC following enrollment of a sentinel cohort of 60 participants. Thereafter, if no clinically significant safety signals are identified, enrollment will resume with the E-DMC conducting frequent safety reviews as outlined in the E-DMC Charter.

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

A dosing regimen of 300 mg PF-07321332 coadministered with 100 mg ritonavir q12h administered orally for 5 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 the first dose of 300 mg of PF-07321332 coadministered with 100 mg ritonavir q12h, median C_{trough} of unbound (free) PF-07321332 are 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.

The selected duration is based on the effectiveness demonstrated following 5-day administration of other antiviral agents used in the treatment of acute respiratory infections, such as remdesivir for SARS-CoV-2 and oseltamivir for influenza.

Preliminary safety data from study C4671001, collected up to 07 April 2021 and 14 April 2021, 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 regimen of 300 mg PF-07321332 coadministered with 100 mg ritonavir q12h administered orally for 5 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 as shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreener 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, and race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

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

    - WOCBP may be enrolled.

    - 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. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization.

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

3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization (see Appendix 9 for criteria).

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

   - ≥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 ≥20 mg 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 provided the participant does not meet Exclusion Criterion 5;
   - 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 trial period;
- Medical-related technological dependence (eg, CPAP [not related to COVID-19]).

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

Informed Consent:

6. 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 hospitalization for the medical treatment of COVID-19.

2. Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator (see Section 8.1.2.)

3. Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection.

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

5. Receiving dialysis or have known moderate to severe renal impairment [ie, eGFR <45 mL/min/1.73 m^2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula].[30]

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

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

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. History of 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 or is expected to receive convalescent COVID-19 plasma.

14. Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit.

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 long-term follow-up visit.

Prior/Concurrent Clinical Study Experience:

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

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

Diagnostic Assessments:

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

    - AST or ALT level ≥2.5 X ULN;
    - Total bilirubin ≥2 X ULN (≥3 X ULN for Gilbert's syndrome);
    - Absolute neutrophil count <1000/mm^3.
    - GFR <45 mL/min/1.73 m2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula[30]

    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.

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

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

Other Exclusions:

20. Females who are pregnant or breastfeeding.

21. 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 (or PF-07321332 100 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, 100 mg	0 mg	100 mg	0 mg

Study Interventions(s)				
Dosage Level(s)	300 mg q12h for 5 days	0 mg q12h for 5 days	100 mg q12h for 5 days	0 mg q12h for 5 days
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 required per country requirement. Products will be provided with blinded labels.	Study intervention will be provided in blister wallets. Each wallet will be labeled as required per country requirement.	Study intervention will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in 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	Placebo
Arm Type	experimental	placebo
Arm Description	Participants will receive PF-07321332/ritonavir 300 mg/100 mg every 12 hours for 5 days.	Participants will receive 0 mg every 12 hours for 5 days
Associated Intervention Labels	PF-07321332/ritonavir	Placebo

6.1.1. Administration

PF-07321332 150 mg tablets or placebo for PF-07321332, will be administered for 5 days with ritonavir 100 mg or placebo for ritonavir capsules. Participants will be dispensed 1 blister wallet of PF-07321332 150 mg or placebo for PF-07321332 tablets and 1 bottle of

ritonavir or placebo for ritonavir capsules. Participants will be given clear dosing instruction to take:

- 2 tablets of PF-07321332 150 mg or placebo for PF-07321332 q12h
- 1 capsule of ritonavir 100 mg or placebo for ritonavir q12h.

For the sentinel cohort only (Phase 2): Some participants in this sentinel cohort may receive PF-07321332 100 mg tablets or placebo for PF-07321332. In this instance, PF-07321332 100 mg tablets or placebo for PF-07321332 will be administered for 5 days with ritonavir 100 mg or placebo for ritonavir capsules. Participants will be dispensed 1 blister wallet of PF-07321332 100 mg or placebo for PF-07321332 tablets and 1 bottle of ritonavir or placebo for ritonavir capsules. Participants will be given clear dosing instruction to take:

- 3 tablets of PF-07321332 100 mg or placebo for PF-07321332 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 (or 3 tablets of PF-07321332 100 mg tablets, if sentinel cohort) or placebo and 1 capsule of ritonavir 100 mg or placebo at the same time. 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 drug in order to "make up" what had been missed. Dosing should be stopped at the end of the treatment period (10 doses total). Any remaining tablets and/or capsules at the end of 5 days (or 6 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.

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 visits summarized in the SoA.

Returned study intervention must not be redispensed to the study 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 at a minimum a clinician, statistician and programmer(s) and will be separate from the blinded members of the study team.

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments.

Unless efficacy is demonstrated at an interim analysis, the study will be unblinded after all participants complete the Day 34 visit (or ET prior to Day 34 visit), and analyses through Day 34, including the primary efficacy endpoint analyses, will be conducted.

Details of the unblinded sponsor staff supporting the 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) 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 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/placebo or ritonavir/placebo 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/placebo greater than 900 mg or ritonavir/placebo greater than 300 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the 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 may receive SoC therapy for COVID-19, in addition to study intervention, unless listed as prohibited medication (see Appendix 8) or as defined in Section 5.2. SoC therapy is defined as any therapy that is approved and used as indicated by the local

regulatory authorities (including approvals for emergency use, compassionate use, or through similar regulatory guidance), or any therapy as recommended by a relevant national (or a reputable international) scientific body (eg, WHO, ECDC, CDC, NIH). Sites should consult with the sponsor if a new SoC option becomes available after study initiation. Investigator should ensure that any recommended SoC therapy is not a strong inducer of CYP3A4 or highly dependent on CYP3A4 for clearance.

In countries in which mAb are authorized or approved and considered the SoC, all participants will be referred locally for treatment with mAb as deemed appropriate by the investigator and local guidelines and this referral should be documented. Notwithstanding, this mAb treatment is not mandatory for participation in this study.

Prohibited During the Study

Participants should not receive convalescent COVID-19 plasma treatment for COVID-19, during the study period. COVID-19 vaccinations are permitted after the Day 34 visit.

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 of PF-07321332.

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 before the first dose of study intervention is administered 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 of Grade 3 severity or greater and considered by the investigator to be related to study intervention;
- SAE considered by the investigator to be related to study intervention;
- Requirement for prohibited concomitant medication;
- Death;
- Pregnancy;
- Study terminated by sponsor;
- Withdrawal by participant or legally authorized representative
- Miss more than 2 consecutive doses of study intervention.

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

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 postscreening 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.

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 150 mL. There will be an additional optional up to 4 mL of blood collected for a subset of participants who agree to collect an optional PK sample. 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 will use 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. 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.

Hospitalization is defined as >24 hours 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 purposes of public health and/or clinical trial execution.

8.1.3. 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 described in Section 8.1.1.

COVID-19-related symptoms will be evaluated in accordance with FDA guidelines (Appendix 10).[31] Participants will record a daily severity rating of their symptom severity over the past 24 hours based on a 4-point scale in which 0 is reported if no symptoms were present; 1 if mild; 2 if moderate; and 3 if severe.

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

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

Targeted COVID-19-associated symptoms are a subset of these symptoms (Appendix 9).

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. PRO Assessments

8.1.5.1. Global Impression Questions

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

8.1.5.2. WPAI

COVID-19 impacts manual and office-based work, and results in missed work due to illness or quarantine and loss in of productivity.[32] The Work Productivity and Activity Impairment Questionnaire: General Health (GH) is being implemented for COVID-19 (ie., WPAI-COVID-19) in order to evaluate change from baseline in work burdens. The WPAI-GH has demonstrated validity, reliability and sufficient predictive value to measure the impact of

disease on absenteeism, presenteeism, and overall productivity in a manner that can also be monetized.[33]

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

8.1.5.3. 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 health technologies assessment (HTA).[34-36] Recently, a version was developed called EQ-5D-5L with 5 response levels on each dimension compared to the 3 response levels in the Euroquol Quality of Life 5-Dimension 3-Level Scale (EQ-5D-3L).[34-40]

Measurement properties of the EQ-5D-5L demonstrated to be a valid version of the 3 level questionnaire that improved measurements by adding discriminatory power, reducing the ceiling, and establishing convergent and known groups validity.[34,36,38,39] Both the EuroQol EQ-5D-3L and EQ-5D-5L versions are well established instruments used to measure health states and utilities in various diseases areas and assess mobility, self care, usual activities, pain/discomfort, anxiety/depression and health status using a VAS.[37,41] The EQ-5D-5L should be completed as described in the Schedule of Activities.

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

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

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).

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

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

8.2.5. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. Triplicate 12-lead ECGs obtained at a minimum at baseline/Day 1, should be obtained approximately 2 to 4 minutes apart.

ECG data may be submitted to a central laboratory for measurement. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (Appendix 7) and should be evaluated further, as clinically warranted

If a) a postdose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QT value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring.

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

ECG values of potential clinical concern are listed in Appendix 7.

8.2.6. 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[42], 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.

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.

8.2.7. 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). 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

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.

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

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 1.5 mL plasma, will be collected for measurement of plasma concentrations of PF-07321332 as specified in the SoA. In a subset of participants, additional optional PK samples may be collected via home health visit, in-clinic visits, or self-collected whole blood microsample (Tasso device) 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 does not apply to samples that are specified to be collected "at any time."

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 concentration of ritonavir.

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

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

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

8.5. Genetics

8.5.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

CCI [redacted]

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:

- NP/nasal swab will be collected to measure SARS CoV-2 viral load by RT-PCR.
- Residual NP/nasal viral load samples may be used for SARS CoV-2 viral sequencing.
- Residual NP/nasal viral load samples may be used for SARS CoV-2 infectivity assays and phenotypic analyses.

CCI [redacted]

8.6.1. Specified Gene Expression (RNA) Research

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

CCI [redacted]

8.6.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.6.4. Viral Load Assessments

An NP/nasal swab will be collected per the SoA, and may be analyzed to measure SARS-CoV-2 RNA by RT-PCR. Residual viral load samples may be utilized for viral sequencing to assess for signs of viral evolution and evaluation of potential genetic viral variants

(eg, 3CL gene) or immune responses, SARS CoV-2 infectivity assays, and additional molecular analysis.

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

CCI [redacted]

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 to be tested is whether or not there is a difference in proportion of participants with COVID-19 related hospitalization (as defined in Section 8.1.2) or death from any cause through Day 28 between PF-07321332/ritonavir and placebo. The statistical hypothesis is as follows:

$$\left.\begin{array}{l} \text{Ho: } \pi_{\text{PF-7321332}} - \pi_{\text{placebo}} = 0 \\ \qquad \textit{versus} \\ \text{Ha: } \pi_{\text{PF-7321332}} - \pi_{\text{placebo}} \neq 0 \end{array}\right\} \quad (1)$$

Where $\pi_{\text{PF-07321332}}$ and π_{placebo} are the proportion of participants with hospitalization or death through Day 28.

Following the positive test of the primary endpoint, sequential testing will be performed for the following 2 secondary endpoints:

1. Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 who did not receive COVID-19 therapeutic mAb treatment, regardless of their onset of COVID-19 related signs and symptoms.

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

Other secondary endpoints will be subsequently tested following the Hochberg procedure.[43]

9.1.1. Estimands

9.1.1.1. Primary Estimand/Co-Primary Estimands

The primary estimand is the difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult participants with symptomatic COVID-19 who are at increased risk of progression to severe disease (as defined in Section 5.1), who did not receive COVID-19 therapeutic mAb treatment, and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.

9.1.1.2. Secondary Estimands

The estimand associated with the key secondary efficacy objective is the difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomized treatment.

The estimand associated with the secondary efficacy objective regarding the duration and severity of signs and symptoms is the absolute difference in median time to sustained

alleviation or resolution of symptoms for all nonhospitalized adult patients with COVID-19 who are at increased risk of progression to severe disease. This will be estimated irrespective of adherence to randomized treatment.

The hospitalization/death rate through Day 28 is considered the main clinical outcome measure and signs/symptom duration is considered key secondary for this study and so estimands for these measures are presented. Estimands for the other outcome measures that are considered supportive of the primary outcome measures and of the sign/symptoms duration and severity outcome measure are not presented.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Full Analysis Set (FAS)	All participants randomly assigned to study intervention.
Safety Analysis Set (SAS)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they received.
Modified Intent-To-Treat (mITT)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 postbaseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment, and were treated ≤3 days after COVID-19 symptom onset. Participants will be analyzed according to the study intervention to which they were randomized.
Modified Intent-To-Treat1 (mITT1)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 postbaseline visit through Day 28 and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment. Participants will be analyzed according to the study intervention to which 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 with at least 1 postbaseline visit through Day 28. Participants will be analyzed according to the study intervention to which they were randomized.
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

Participant Analysis Set	Description
	exclusion criteria will be finalized prior to breaking the blind.

For the primary efficacy analysis, the mITT set will be used and will be the primary analysis. A secondary analysis of the primary endpoint will be performed and will use the mITT2 analysis set. For all other efficacy analyses, mITT, mITT1 and mITT2 sets will be used, as defined in the SAP. The PP analysis set will be used in the analyses of primary efficacy endpoint. The Safety Analysis Set will be used in the analyses of the safety data.

9.3. Statistical Analyses

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

9.3.1. General Considerations

Descriptive statistics for all efficacy endpoints by treatment group and visit will be provided.

The number of participants screened, 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 all 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 (with the corresponding sample sizes).

For continuous endpoints, an MMRM analysis of covariance model will be used to analyze change from baseline over time. Estimated mean differences between treatments and their respective 95% CI and p-values will be calculated.

For binary endpoints, proportion of participant with the event will be summarized for each group. Treatment comparison between the group will be presented as the difference of proportions with its 95% confidence interval using a similar analysis method as the primary endpoints.

For categorical endpoints, proportion of participant 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.

For time-to-event endpoints (ie, time [days] to sustained alleviation/resolution of all targeted signs/symptoms through Day 28 and duration of each targeted COVID-19 sign/symptom),

2 analyses will be provided: (1) a Cox proportional hazard regression model where the estimate of the hazard ratio for treatment (PF-07321332 vs placebo), its CI, and p-value will be provided; and (2) Kaplan-Meier analysis where tabular summaries of the Kaplan-Meier curves providing the median, quartiles, and range will be provided for each treatment group. In addition, the KM curves will be presented graphically.

Imputation of missing data within efficacy variables and endpoints will be computed according to the rules specified in the SAP.

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

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

The cumulative proportion of participants hospitalized for the treatment of COVID-19 or dying during the first 28 days of the study will be estimated for each treatment group using the Kaplan-Meier method to take account of losses to follow-up and summarized graphically for each treatment group. The estimand is then the difference of the proportions in the 2 groups and its 95% CI will be presented, as well as, the associated Wald Test. For the 95% CI, the corresponding estimate of the standard error is computed using Greenwood's formula.[1] The Greenwood's formula to estimate the variance of the difference of proportions at Day 28 is [$Var(S_{PF}(28)) + Var(S_{Placebo}(28))$]. Instead of dealing with $S(t_i)$ the log-log approach to CI will be used. The 95% CI will be computed for the estimate of $L(t)= \log(-\log(S(t))$, the log hazard function.

The CI will be in the right range when transformed back to $S(t) = \exp(-\exp(L(t))$. Antilogging this CI will give a 95% confidence interval for the difference itself.

The above primary analysis will be conducted for the planned interim analysis as well. Two-sided 95% CI (adjusted for the planned interim analysis) and associated p-value for the null hypothesis of no difference between treatment groups will be presented. Significance level will be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall significance level is set at 5% (2 sided).

For participants who complete Day 28 assessment (Day 34), they will be censored at their last visits. For participants who discontinue before Day 28 assessment or are lost to follow up, they will be censored at the last known date in the study.

The secondary analysis associated with primary endpoint will be conducted using the mITT2 population set.

Supplemental analyses will be performed to the primary efficacy endpoint:

1. An analysis in the mITT analysis set of the primary endpoint where participants that received a therapeutic COVID-19 mAb treatment post-baseline will be considered as an event for the endpoint (in addition to hospitalization for COVID-19 and death due to any cause) with mAb treatment date as the time of event.

2. A logistic regression model will be fitted to the primary endpoint of hospitalization/death and will include treatment and effect based on investigator site as independent variables (p-values will be reported from main model). Additional analyses may be performed adjusting for baseline covariates (such as age, gender, etc.) as additive terms to the primary model, if necessary.

3. A completers (participants with Day 28 assessment) only analysis similar to the primary efficacy analysis will be conducted.

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

Proportion of participants with COVID-19 related hospitalization or death due to any cause through Day 28

The first key secondary efficacy endpoint is the proportion of participants with COVID-19 related hospitalization or death due to any cause through Day 28 in the mITT1 analysis set. The analysis for this endpoint is similar to the primary endpoint, but using the mITT1 analysis set.

Time to sustained alleviation and time to sustained resolution of targeted COVID-19 sign/symptoms through Day 28

The key secondary endpoints of sustained alleviation and resolution will be defined for all targeted COVID-19 associated symptoms based on self-assessment.

Sustained alleviation of all targeted COVID-19 signs/symptoms is defined as the event occurring on the first of 4 consecutive days when all symptoms scored as moderate or severe at study entry are scored as mild or absent AND all symptoms scored mild or absent at study entry are scored as absent. The first day of the 4 consecutive-day period will be considered the First Event Date.

Sustained resolution is defined as when all targeted symptoms are scored as absent for 4 consecutive days. The first day of the 4 consecutive-day period will be considered the First Event Date.

For any symptoms not present at baseline, it must be absent at the last possible available day (prior to or at Day 25) to be counted as sustained alleviation/resolution. For symptoms with no reported severity in baseline, the symptom will have to be absent in order to consider alleviated/resolved (missing severity at baseline will be treated as mild).

Day 25 is the last possible day the symptom alleviation and resolution endpoints can be achieved (definition includes data from the subsequent three days) and Day 28 is the last day participants report their daily signs and symptoms.

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

- For a participant with sustained symptom alleviation/resolution (event), time to event will be calculated as (First Event Date) – (First Dose Date) +1.

- For a participant that either completes Day 28 of the study or discontinues from the study before Day 28 without sustained symptom alleviation/resolution (censored), censoring date will be at the last date on which symptom alleviation/resolution is assessed, and time will be calculated as (Censoring Date) – (First Dose Date) +1 or day 25 whichever occurs first.

The decision to require 4 consecutive days with all targeted symptoms absent was based on exploratory analyses of data from the ACTIV-2/A5401 study, which suggested that this choice (rather than requiring fewer consecutive days) better captured sustained symptom resolution with low probability of subsequent relapse.

Participants who are hospitalized for the treatment of COVID-19 or die from any cause during the 28-day period will be classified as not achieving sustained symptom alleviation/resolution and will be censored at day 25.

Cox proportional hazard model analyses will be used for time to sustained symptom alleviation/resolution.

Time to sustained symptom alleviation/resolution will be summarized graphically using Kaplan-Meier plots for each of the treatment groups, the analyses will be done using mITT population, mITT1 population, and the mITT2 population.

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

- Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28

- Duration of each targeted COVID-19 sign/symptom

- Progression to a worsening status in 1 or more self-reported COVID-19 associated symptoms through Day 28

- Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.

- Proportion of participants with death (all cause) through Week 24

- PK of PF-07321332
- Viral titers (RT-PCR) measured in nasal swabs over time
- Number of COVID-19 related medical visits through Day 28.
- Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.

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

CCI [redacted]

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

All 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

All physical examination and vitals will be descriptively summarized by treatment group.

CCI [redacted]

Long-term COVID-19 symptoms will be collected by telephone interviews at Weeks 12 and 24 and PRO data (Global impression questions, EQ-5D-5L, WPAI) will be collected during the trial. These data 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 collected in a subset of participants via home health, site visit, or self-collected 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

A planned interim analysis for efficacy and futility with a sample size-re-estimation will be conducted and reviewed by an independent E-DMC after approximately 45% overall participants have completed the Day 28 assessments in the mITT analysis set (ie, 28 days after randomization).

At the time of planning the Phase 2/3 study, there was uncertainty about the rate of COVID-19-related hospitalization or death in the primary analysis population, and about the treatment effect of PF-07321332. Hence, a sample size re-estimation will be conducted during the interim analysis based on conditional power. The sample size can be adjusted one time and the increase will be capped at 30%. A well-established method described by Cui, Hung, and Wang (1999)[44] (implemented in EAST 6.5) will be used to control the Type I error probability.[45]

The nominal significance level for the planned interim and final proportion of hospitalization/death analyses is determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary, with an overall 2-sided type I error rate of 5%.

For the interim analysis (45%), O'Brien-Fleming approach will be used for decision making, ie, reject H_0 with 2-sided p-value ≤0.002, or reject H1 with 2-sided p-value >0.924. The final p-value for rejecting H_0 will be ≤0.049 (2-sided) or reject H1 with 2-sided p-value >0.049. The actual stopping boundaries will depend on the exact timing of the interim analysis. If the efficacy boundary is crossed at the interim analysis, a final analysis will be conducted as a supportive analysis.

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 an E-DMC Charter. In addition, the analysis details will be documented and approved in the SAP.

9.5. Sample Size Determination

The estimate of required sample size is based on data from the BLAZE-1 Phase 2/3 trial among participants with mild to moderate COVID-19 who were at high risk for progressing to severe COVID-19 and/or hospitalization at enrollment.[2] During the 29-day period following enrollment, the proportion of placebo-treated participants with a COVID-19-related hospitalization/emergency department visit was 7% in the Phase 3 portion of the trial.[3]

This study is designed to have 90% statistical power to show a difference of 3.5% in the proportion of participants hospitalized/dying that did not receive COVID-19 therapeutic mAb between the treatment arms (PF-07321332/ritonavir versus placebo) and were treated ≤3 days after COVID-19 symptom onset, using a 2-sided Type I error rate of 5%. Based on the above study,[3] the proportion of hospitalization/death in the placebo arm is assumed to be 7%.

Using EAST (Version 6.5) for a 2-sample proportion test[44], the sample size needed to detect this difference with 90% power at a 2-sided significance level of 5% was determined to be 1717 randomized participants. Enrollment of participants that have received/expected to receive COVID-19 therapeutic mAb treatment is expected to be approximately 20% and will be limited to approximately 25% of participants. Enrollment of participants that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25% and will be limited to a total of approximately 1000 participants. Assuming a 5% dropout rate, the total sample size for this study will be approximately 3000 participants.

Study enrollment will be stopped after approximately 1717 participants are available for the primary analysis.

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

10.1.3. Informed Consent 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.

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

- Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 60 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.

- Proof-of-concept assessment: The E-DMC will review viral load data when approximately 200 participants in the primary analysis set with evaluable data complete the Day 5 assessments. Enrollment will not be paused during review of these data but may be paused or stopped following E-DMC review.

- Interim analysis: A planned interim analysis for efficacy and futility with a sample size re-estimation will be done after approximately 45% of participants in the mITT set complete the Day 28 assessments (ie, 28 days after randomization).

The E-DMC will also review the results of planned interim analysis. Efficacy data will be available to the E-DMC for the interim analysis. Details of the E-DMC are specified in the E-DMC Charter.

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 Thyroid function TSH T4 (free) Coagulation PT/aPTT Fibrinogen D-dimer SARS-CoV-2 serology (IgM, IgG) 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.[30]
b. FSH testing is performed locally 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 <u>Meeting</u> the AE Definition

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding,	All AEs 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

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.

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,[42] 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 nonhormonal method of contraception must also be used if the participant is using estradiol-containing contraceptives.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

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

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

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

- The samples will be retained as indicated:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede 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

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

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

ECG Findings That Qualify as SAEs

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

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

10.8. 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.

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-infectives	Rifampin	Reduced concentrations of PF-07321332/ritonavir; may result in suboptimal concentrations
Anticonvulsants	Phenytoin, Carbamazepine	
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	Analgesic concentrations may increase
Antianginal	Ranolazine	Risk of cardiac arrhythmias
Antiarrhythmics	Dronedarone	Risk of cardiac arrhythmias
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	Triazolam, oral midazolam	Risk of prolonged sedation, respiratory depression, or hypnotic concentrations
Miscellaneous Drugs	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.

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-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	Tamsulosin, silodosin, doxazosin (>2 mg daily), terazosin (>5 mg daily),	Risk of hypotension, syncope
Analgesics Opioid Dependence Treatment Anesthetic	Methadone Fentanyl, oxycodone Buprenorphine Lofexidine Pethidine (Meperidine)	Moderate to weak decreases in methadone concentrations have been observed Analgesic concentrations may increase Co-administration may increase concentrations of buprenorphine and lofexidine Co-administration with ritonavir may result in increase in concentration of the metabolite normeperidine
Antiarrhythmics	Amiodarone, Bepridil, Flecainide, Propafenone, Quinidine, Encainide, Disopyramide, dofetilide, lidocaine, mexiletine	Risk of cardiac arrhythmias
Anticoagulants/ antiplatelet	Rivaroxaban, Vorapaxar, apixaban, betrixaban, dabigatran, edoxaban ticagrelor Warfarin	Possible increased risk of bleeding Possible decreased warfarin effects
Anticonvulsants	Ethosuximide Eslicarbazepine Oxcarbazepine Phenobarbital Lamotrigine Divalproex Valproate	Co-administration may increase these anticonvulsant concentrations or decrease PF-07321332 and ritonavir concentrations Co-administration may decrease concentration of lamotrigine, divalproex, and valproate

Prohibited Medications Dependent on CYP450 3A4 for Clearance or with other Notable Interactions[a] These medications are prohibited ***from 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**
Antidepressant	Desipramine, Fluoxetine, Paroxetine nefazodone, Amoxapine, Clomipramine, Doxepin, Imipramine, Maprotiline Amitryptiline, nortryptiline, protryptiline, Trimipramine, aripiprazole	May increase antidepressant concentration
Anti-infective (antibacterials)	Erythromycin	Co-administration may increase erythromycin concentrations.
	Clarithromycin	Co-administration may increase clarithromycin concentrations.
(antimycobacterials)	Bedaquiline	Co-administration may increase bedaquiline concentrations
	Rifabutin	Co-administration may increase rifabutin concentrations
(antifungals)	Isavuconazole Itraconazole Posaconazole Ketoconazole Voriconazole	Possible increased concentrations of antifungal, of PF-07321332, or both. Co-administration of ritonavir with voriconazole may result in reduction in voriconazole levels
Antihistamines	Astemizole, Terfenadine	Risk of cardiac arrhythmias
Antipsychotics	Quetiapine Risperidone, Perphenazine, aripiprazole, brexpiprazole, cariprazine, Iloperidone, perphenazine, risperidone, thioridazine, ziprasidone	Co-administration may increase quetiapine and increase risk of quetiapinerelated toxicity. 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-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**
(calcium channel blockers)	Diltiazem, Verapamil, Nifedipine, amlodipine (> 5 mg daily)	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.
(cardiac glycosides)	Digoxin	Co-administration increases digoxin concentrations.
	Eplerenone	Co-administration increases eplerenone concentrations
	Ranolazine	Co-administration increases ranolazine 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

Prohibited Medications Dependent on CYP450 3A4 for Clearance or with other Notable Interactions[a] These medications are prohibited ***from 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**
Ergot Derivatives	Ergonovine	Risk of acute ergot toxicity (peripheral vasospasm and ischemia of the extremities)
Hepatitis C direct acting antivirals (DAAs)	Boceprevir, Glecaprevir/Pibrentasvir Simeprevir, Sofosbuvir/Velpatasvir/Voxilaprevir, Ombitasvir/Paritaprevir/ritonavir/ Dasabuvir, Grazoprevir/elbasvir	Co-administration can increase plasma concentrations of select DAAs
HIV Antiretrovirals Protease Inhibitors	Lopinavir, Amprenavir, Indinavir, Nelfinavir, Atazanavir, Darunavir, fosamprenavir, saquinavir, tipranavir. Ritonavir or cobicistat containing combination products	Co-administration may increase HIV protease inhibitor concentrations. 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
Lipid lowering drugs (HMG-CoA Reductase Inhibitors)	Atorvastatin (>20 mg daily), Rosuvastatin (>10 mg daily) Lomitapide	Risk of rhabdomyolysis Co-administration may increase concentration of lomitapide
Hypoglycemics	Glipizide, Tolbutamide Repaglinide Saxagliptin (>2.5 mg daily)	Potentially decrease glipizide and tolbutamide concentrations Potentially increase repaglinide concentrations Co-administration may increase saxagliptin concentration
Immunosuppressants	Cyclosporine, Tacrolimus, Sirolimus, everolimus	Co-administration may increase immunosuppressant concentrations

Prohibited Medications Dependent on CYP450 3A4 for Clearance or with other Notable Interactions[a] These medications are prohibited ***from 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**
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
Neuroleptic	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
Miscellaneous Drugs	Cisapride	Co-administration may result in increased cisapride concentration and possible cardiac arrhythmias
	Dronabinol	Co-administration may increase dronabinol concentration
	Eluxadoline (>75 mg twice daily)	Co-administration may increase eluxadoline concentration
	Flibanserin	Co-administration may increase flibanserin concentration.

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

Hormonal Contraceptives: Estradiol-containing hormonal contraceptive medications can be continued while receiving investigational product, but their effectiveness may be impacted. Therefore, barrier methods of contraception must be used for at least one full menstrual cycle following completion of investigational product dosing.

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	No data available
	Sertraline, Bupropion Trazodone	Co-administration may decrease sertraline and bupropion concentrations Co-administration with ritonavir increases the level/effect of trazodone by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Further, trazodone may decrease the level/effect of ritonavir by P-glycoprotein (MDR1) efflux transporter. To be used with caution.
Anticancer Agents:	Dasatinib, imatinib, nilotinib, venetoclax, Vincristine, Vinblastine	Co-administration of ritonavir may increase the concentration of dasatinib and nilotinib. Coadministration of ritonavir with venetoclax may increase concentration of venetoclax and increase the risk of tumor lysis syndrome. Con-administration with ritonavir may increase the concentrations of vincristine and vinblastine and develop significant hematologic or gastrointestinal side effects.
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

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**
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	RTV 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
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

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**
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 Attributable to COVID-19

Table 2. Signs and Symptoms Attributable to COVID-19

Daily Sign and Symptom Collection[31]	Entry Criterion#3 Targeted (used for study entry)	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
Chills or shivering	X	X	X
Fatigue (low energy or tiredness)	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	
Loss of taste		X	

10.10. Appendix 10: Country-Specific Requirements

10.10.1. France

Contrat Unique

1. GCP Training

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

2. Study Intervention

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

3. Urgent Safety Measures

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

4. Termination Rights

   Pfizer retains the right to discontinue development of PF-07321332 at any time.

10.10.2. Japan

A Protocol Administrative Change Letter was issued on 22 July 2021 to provide Japan country specific guidance regarding Exclusion Criterion #6 .

Exclusion Criterion #6: 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.

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10.11. Appendix 11: Protocol Amendment History

Amendment 1 (02 July 2021)

Overall Rationale for the Amendment: The protocol was amended to incorporate regulatory feedback.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis Section 3.0 Objectives, Endpoints and Estimands Section 9.3.4 Secondary Endpoint(s)/Estimand(s) Analyses	Removal of COVID-19 severity ranking endpoint.	To address regulatory feedback.
1.1 Synopsis Section 3.0 Objectives, Endpoints and Estimands Section 9.3.4 Secondary Endpoints	Secondary endpoint related to medical visits will include hospitalizations.	To align with program strategy.
1.2 Schema	Schema footnote was updated.	For clarification.
1.3 Schedule of Activities Section 8.1.5.1 Global Impression Questions Section 9.3.7 Other Analyses	Addition of 3 global impression questions to be added to the ePRO daily and collected in participants after the sentinel cohort as available.	To address regulatory feedback.
Section 5.1 Inclusion Criteria	Window for positive RT-PCR test updated to 5 days in inclusion criteria. New wording: Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization.	To improve operational feasibility.
Section 5.2 Exclusion Criteria	Exclusion criterion updated with new wording: Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection.	For clarification.
Section 9	Clarifications made to text in statistical section.	To address regulatory feedback.
Section 9.2 Analysis Sets	Updated mITT1 definition.	To address regulatory feedback.
	Typographical errors were corrected and minor edits were made.	For clarification and to ensure consistency.

Amendment 2 (02 August 2021)

Overall Rationale for the Amendment: The primary analysis set (mITT) has been refined to include just those participants who were treated ≤3 days after COVID-19 symptom onset (mITT). There is precedent for early treatment of acute respiratory illnesses being critical for successful antiviral intervention. This change allows for optimization of the primary analysis set by further reducing the symptom onset window from <5 days to ≤3 days.

Section # and Name	Description of Change	Brief Rationale
Synopsis	Describes changes made in Sections 3, 4 and 9 below.	To summarize changes made in the document.
Section 1 Schedule of Activities	Minor edits to footnotes.	To clarify use of brackets and procedure requirements associated with the location for expected visits.
Section 3 Objectives, Endpoints and Estimands	• Primary estimand changed to specify inclusion of participants who did not receive COVID-19 therapeutic mAbs and who were treated ≤3 days after COVID-19 symptom onset. • A key secondary efficacy endpoint (proportion of participants with COVID-19-related hospitalization or death due to any cause through Day 28) was added.	• Due to uncertainty on the effect of time from symptom onset relative to initiation of treatment on the effectiveness of an antiviral, a change has been made to the primary analysis set. Primary analysis is now based upon the mITT, which includes those participants treated ≤3 days after COVID-19 symptom onset. • The key secondary efficacy endpoint was added as a consequence of the change in primary efficacy analysis and the analysis will include participants regardless of their symptom onset.
Section 4 Study Design	Sample size to be increased from 2260 to approximately 3000 participants.	Changes are a consequence of the change in primary efficacy analysis. The primary efficacy analysis set has been refined to include just those participants who were treated ≤3 days after COVID-19 symptom onset (mITT). Sample size has been adjusted, and the analysis of all participants is now a secondary analysis.
Section 6 Study Intervention(s) and Concomitant Therapy	Guidance added regarding shipping study intervention by courier and temperature monitoring for ground transportation.	Stability data demonstrate that if the total duration of transit is less than 24 hours, temperature monitoring is not required.
Section 6 Blinding of the Sponsor	Language was added to clarify that the study will be unblinded	To provide additional information and clarification in the process of unblinding.

Section # and Name	Description of Change	Brief Rationale
	after all participants have completed the Day 34 visit.	
Section 8 Assessments and Procedures	Text updated to make statement consistent with the SoA regarding follow-up pregnancy test being at Day 34 visit.	Correction made to Section 8 that follow-up pregnancy test is not at end of study, but rather is at Day 34 visit.
Section 9 Statistical Considerations	• Primary estimand changed to specify patients who did not receive COVID-19 therapeutic mAb, and who were treated ≤3 days after COVID-19 symptom onset. • mITT analysis set added that includes participants who did not receive nor were expected to receive COVID-19 therapeutic mAb, and who were treated ≤3 days after COVID-19 symptom onset. • Changed the analysis set for the primary efficacy analysis from mITT1 to mITT. Key secondary efficacy endpoint was added and analysis will be conducted using the mITT1 analysis set. • Enrollment of participants that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25% and will be limited to approximately 1000 participants. • Updated total sample size (from 2260 to approximately 3000 participants).	Due to uncertainty on the effect of time from symptom onset relative to initiation of treatment on the effectiveness of an antiviral, a change has been made to the primary analysis set. Primary analysis is now based upon the mITT, which includes those participants treated ≤3 days after COVID-19 symptom onset. Additional section changes are a consequence of the change in primary efficacy analysis. Primary efficacy analysis set is now based on participants treated ≤3 days after COVID-19 symptom onset. Sample size has been adjusted and the key secondary efficacy endpoint analysis will include participants regardless of their symptom onset.
Section 10 Supporting Documentation and Operational Considerations	Age for those postmenopausal females requiring FSH test at screening updated from under 60 years to under 50 years to be consistent with the SoA	For clarification and to ensure consistency.
Appendix 10	Added Japan country-specific guidance regarding Exclusion Criterion #6.	To incorporate country-specific changes into the global protocol.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Typographical errors were corrected and minor edits were made.	For clarification and to ensure consistency.

Amendment 3 (26 October 2021)

Overall Rationale for the Amendment: To include an additional planned interim analysis for efficacy and futility to be done after approximately 70% of participants in the mITT analysis set complete the Day 28 assessments (ie, 28 days after randomization).

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Describes changes made in Sections 4 and 9 below. • Correction made in description of the first interim analysis to show that it was planned for efficacy and futility, rather than efficacy and safety. • Primary Endpoint(s)/Estimand(s) Analysis: updated to include primary analysis conducted for 2 planned interim analyses. • Added *approximately* to the following statement: Enrollment of participants that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25%, and will be limited to a total of approximately 1000 participants • Sample Size Determination: text updated: To allow for a 5% dropout rate, enrollment will be stopped after approximately 1870 participants have been enrolled to ensure at least 1779 participants are available for the primary analysis. • Sample size increased from approximately 3000 participants to approximately	To summarize changes made in the document.

Section # and Name	Description of Change	Brief Rationale
	3100 participants due to addition of second interim analysis.	
Section 1.2 Schema	• Added new Schema per PACL 12 August 2021	To correct a formatting error.
Section 1.3 Schedule of Activities	• Information added from 12 August 2021 PACL under "other laboratory assessments" • Clarifications made to Day 1 and Day 5 PK sample collection text. • ET pregnancy added. • Text added to clarify that targeted physical examinations will be completed at the following in-person visits: Days 14 and 34, and ET (prior to Day 34). • Text from Section 7.1.1 repeated in this section to clarify that post screening eGFR result of <45 mL/min/1.73m^2 should result in discontinuation of study intervention. • Staff review of study diary added at Days 1 and 3 to ensure that it is reviewed during first few days of study. • Text added to footnotes to clarify that telemedicine visits may be conducted in-person at the discretion of the investigator.	To update as per PACL 12 August 2021 and to clarify other language in the Schedule of Assessments.
Section 2.3.3 Overall Benefit/Risk Conclusion	Text updated to clarify that the 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 and futility at the time of the interim analyses.	To be consistent with the rest of the document.
Section 4.1 Overall Design	• Sample size updated from approximately 3000 participants to approximately 3100 participants due to	To provide a more comprehensive description of the overall study design.

Section # and Name	Description of Change	Brief Rationale
	addition of second interim analysis. • Language added to Section 4.1 information already included in the protocol, in order to describe the expected percentage of participants who will fall in to the mAb treatment group and the capping of participants with symptom onset >3 days. • Added information about the addition of a second interim analysis.	
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 7.1 Discontinuation of Study Intervention	• Updated text about discontinuation of study intervention due to an AE. • Removed requirement to discontinue study intervention if a participant is hospitalized during the active treatment period. • Added that in the event a participant is hospitalized, study intervention may continue to be administered, as feasible, and based on medical judgement of the investigator.	• AE language updated to clarify that not all AEs will result in discontinuation of study intervention. • Updated in order to allow the investigator to use medical judgment to decide whether participant will remain on study intervention during hospitalization.
Section 9 Statistical Considerations	• 9.3.1 General Considerations: Mean and SEM removed from tabular summaries of the Kaplan-Meier curves. • 9.3.2 Primary Endpoint(s)/Estimand(s) Analysis: updated to include primary analysis conducted for 2 planned interim analyses.	With the addition of a second interim analysis while controlling for the overall significance level of 5%, an adjustment is applied to the sample size such that approximately 60 additional participants are needed for the primary analysis resulting in a total of 1779 participants instead of the original 1717 participants. Therefore, the updated total sample size based on this second interim analysis is 3100 participants instead of 3000 participants.

Section # and Name	Description of Change	Brief Rationale
	C C I [redacted] • 9.4. Interim Analyses: Second interim analysis added. • 9.5 Sample Size Determination: text updated: To allow for a 5% dropout rate, enrollment will be stopped after approximately 1870 participants have been enrolled to ensure at least 1779 participants are available for the primary analysis. • Total sample size changed from 3000 to 3100 participants.	
Section 10 Supporting documentation and Operational considerations	• Second interim analysis added.	To add the addition of the second interim analysis to the Data Monitoring Committee description under Committee Structure.
Appendix 8	Updated with information from PACL and additional updates.	Corrections and updates to the list of precautionary and prohibited medications
Throughout the protocol	Typographical errors were corrected and minor edits were made.	For clarification and to ensure consistency.

10.12. Appendix 12: 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
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
bpm	beats per minute
BMI	body mass index
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
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
CYPx	cytochrome P450

Abbreviation	Term
DAA	direct acting antivirals
DAIDS	Division of AIDS
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
dNHBE	differentiated normal human bronchial epithelial cells
DU	dispensable unit
EC	ethics committee
EC_{90}	concentration required for 50% 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
ePRO	electronic patient reported outcome
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
FU	follow up
f_u	fraction of unbound drug in serum or plasma
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GH	good health
GLP	Good Laboratory Practice
HCP	health care professional; health care provider
HCV	hepatitis C virus
HDPE	high-density polyethylene

Abbreviation	Term
HF	heart failure
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl co-enzyme
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
Ig	immunoglobulin
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
IV	intravenous(ly)
IWR	interactive Web-based response
KM	Kaplan Meier
LDH	lactate dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
MAD	multiple ascending dose
MDR1	multidrug resistance mutation
mITT	modified intent-to-treat
MMRM	mixed-effect model repeated measure
msec	millisecond
MRC-5	human lung epithelial cells-5
N/A	not applicable
NHP	non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIMP	noninvestigational medicinal product
NP	nasopharyngeal
PCI	percutaneous coronary intervention
PDE-5	phosphodiesterase

Abbreviation	Term
PK	pharmacokinetic(s)
PP	per-protocol
PRO	patient reported outcomes
PT	prothrombin time
PVC	premature ventricular contraction/complex
q12h	every 12 hours
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
QTL	quality tolerance limit
RBC	red blood cell
RT-PCR	reverse transcription polymerase chain reaction
RTV	ritonavir
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SCR	serum creatinine
SEM	standard error of the mean
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 analogue scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WPAI	Work Productivity and Impairment

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