Title Page

A PHASE 2B, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP, DOSE RANGING STUDY TO EVALUATE VIROLOGICAL RESPONSE AND SAFETY OF ORAL PF-07817883 IN NON-HOSPITALIZED SYMPTOMATIC ADULT PARTICIPANTS WITH COVID-19

Study Intervention Number:	PF-07817883
Study Intervention Name:	NA
US IND Number:	162644
EudraCT Number:	NA
ClinicalTrials.gov ID:	NCT05799495
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5091003
Phase:	2B
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title:

A Phase 2B Study To Evaluate Virological Response and Safety of Oral PF-07817883 in Non-Hospitalized, Symptomatic, Adult Participants With COVID-19.

Document History

Document	Version Date
Amendment 2	14 April 2023
Amendment 1	24 March 2023
Original protocol	01 February 2023

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

Protocol Amendment Summary of Changes Table

Amendment 2 (14 April 2023)

Overall Rationale for the Amendment: To incorporate regulatory feedback on study population eligibility criteria.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Removed inclusion criterion #5, and updated inclusion criterion #2 and exclusion criterion #2 to prohibit enrollment of participants at high risk of progression to severe disease into this study.	To address comments received from the FDA.	Section 1.1 Synopsis, Section 5.1 Inclusion Criteria and Section 5.2 Exclusion Criteria
Edited text to remove reference to participants at high risk of progression to severe disease.	To address comments received from the FDA.	Section 1.1 Synopsis (Ethical Considerations and Exclusion Criterion #12), Section 2.3.2 Benefit Assessment, Section 5.2 Exclusion Criteria and Section 6.9 Prior and Concomitant Therapy.
Added Safety Laboratory Assessments for Blood and Urine at the Day 10 visit.	To address comments received from the FDA.	Section 1.3 SoA
Removed collection of retained research sample	To reduce patient and operational burden by	Section 1.3 SoA, Section 8.6.2 Retained Research Samples for

Description of Change	Brief Rationale	Section # and Name
for genetics (Prep D1) at Day 3, Day 5 and ET visits. Clarified that collection of retained research sample for genetics (Prep D1) and retained research samples for biomarkers (Prep B2.5/R1) is optional.	removing redundant samples (Days 3 and 5 and ET visits) and to address comments received from FDA (change retained research samples from mandatory to optional collections).	Genetics and Section 8.7.6 Retained Research Samples for Biomarkers
Removed Sensitive CYP3A4 Substrates with Narrow Therapeutic Index for alignment with Section 6.9 Prior and Concomitant Therapy.	To address comments received from the FDA.	Section 10.9 Appendix 9: Prohibited Concomitant Medications That May Result in DDI
Removed the sponsors definition of viral RNA rebound.	To address comments received from the FDA.	Section 10.11 Appendix 11: Definition of Viral RNA Rebound
Deleted “or other trial involving PF-07817883” from exclusion criterion #15.	To allow healthy participants from study C5091001 to enroll in this study if they develop COVID-19 at a later date.	Section 1.1 Synopsis and Section 5.2 Exclusion Criteria
Added discontinuation criteria for participants who develop AKI.	To comply with new updated guidance on the evaluation of potential acute kidney injury.	Section 7.1.1 Potential Cases of Acute Kidney Injury
Removed the option for home health visits.	Home health visits were underutilized in previous studies.	Section 1.1 Synopsis, Section 1.3 SoA, Section 4.1 Overall Design, Section 8.1.3 Home Health Visits and Section 8.3.3 Targeted Physical Examinations
Added additional reflex laboratory tests for DIKI in the right column of the table. Added laboratory tests for calculating UACR under “Urinalysis” column.	To comply with new updated guidance on evaluation of potential acute kidney injury.	Section 10.2 Appendix 2: Clinical Laboratory Tests

Description of Change	Brief Rationale	Section # and Name
Non-substantial Modification(s)		
Edited Study Visit Location notes to specify that Day 33 visit should be conducted in-person if a NP sample needs to be collected.	Clarification that if a NP sample needs collecting on Day 33, this must be an in-person visit at the site.	Section 1.3 SoA and Section 8.1.2 Telehealth Visits
Added text to specify that SARS-CoV-2 serology is a part of Other Laboratory Assessment and only Day 1 and Day 10 sample will be assessed for SARS-CoV-2 serology.	Clarification that SARS-CoV-2 serology is evaluated with only Day 1 and Day 10 sample.	Section 1.3 SoA and Section 10.2 Appendix 2: Clinical Laboratory Tests
Edited "through Day 28" to "over time" for the first two tertiary/exploratory endpoints listed.	To better align with SAP reporting and SoA.	Section 3 Objectives, Endpoints, and Estimands
Added reference to viral RNA level assessment at Day 5.	Provide consistency with Section 1.1 Synopsis – Statistical Methods.	Section 4.1 Overall Design
Removed reference to receiving dialysis for exclusion criterion #7.	Removed duplication since Chronic Kidney Disease requiring dialysis is already included in exclusion criterion #2.	Section 5.2 Exclusion Criteria
Edited total blood sampling volume.	To account for the Safety Laboratory Assessments added for Day 10 and the optional Day 21 retained research sample collection.	Section 8.1 Administrative and Baseline Procedures
Added a sentence to clarify the investigator will determine whether medical visits are considered COVID-19-related.	To address comments received from the FDA.	Section 8.2.2 COVID-19-Related Medical Visit Details
Removed collection of previous mAb treatment	CRF will not require that all previous mAb	Section 8.3.1 Medical History

Description of Change	Brief Rationale	Section # and Name
prior to the planned first dose of study drug.	treatment prior to the planned first dose of study drug be documented.	
Addition of a sentence on reporting plan for exploratory endpoints.	Clarification that some exploratory endpoints may not be reported in the CSR.	Section 9.3.4 Tertiary/Exploratory Endpoint(s) Analysis
Added "(urine)" to Albumin Urinalysis assessment.	Clarification that albumin assessment should be from a urine sample.	Section 10.2 Appendix 2: Clinical Laboratory Tests
Edited interim analysis plan specifications and blinding plan.	Clarifications on the planned protocol analysis.	Section 9.4 Interim Analyses
Minor edits in this section.	To comply with new regulatory requirements.	Section 7.1 Discontinuation of Study Intervention
Added NCT number.	ClinicalTrials.gov ID now available.	Title Page
Moved Amendment 1 Summary of Change text and table into new Appendix 12.	To comply with new regulatory requirements.	Section 10.12 Appendix 12: Protocol Amendment History
Minor edits to clarify protocol text and correct minor errors and typos from previous versions.	To clarify protocol text and correct inadvertent errors.	Several sections throughout.

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2B, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Dose Ranging Study to Evaluate Virological Response and Safety of Oral PF-07817883 in Non-Hospitalized, Symptomatic, Adult Participants with COVID-19.

Brief Title:

A Phase 2B Virological Response and Safety Study of PF-07817883 in Non-Hospitalized, Symptomatic, Adult Participants With COVID-19.

Regulatory Agency Identification Number(s):

US IND Number:	162644
EudraCT Number:	NA
ClinicalTrials.gov ID:	NCT05799495
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5091003
Phase:	2B

Rationale:

The purpose of this study is to assess the effect of PF-07817883 on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ribonucleic acid (RNA) level reduction in nasopharyngeal (NP) samples and to evaluate the safety of PF-07817883 treatment in non-hospitalized, symptomatic, adult participants with coronavirus disease 2019 (COVID-19). The study is designed as a dose-ranging study to collect pharmacological and safety information to inform dose selection of PF-07817883 in later stage Phase 2/3 studies.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To describe the effect of PF-07817883 treatment versus placebo on SARS-CoV-2 RNA levels in NP samples in non-hospitalized symptomatic adult participants with COVID-19.	• Change from baseline in SARS-CoV-2 RNA level on Day 5.	• E1: The estimand is the difference between the PF-07817883 dose groups and placebo in mean change from baseline in SARS-CoV-2 RNA level in NP samples in the population of non-hospitalized, symptomatic, adult participants with COVID-19 who have SARS-CoV-2 RNA level ≥ 4 $\log_{10}$ copies/mL at baseline. This analysis will exclude data after use of

Objectives	Endpoints	Estimands
		prohibited COVID-19 medications and after study treatment discontinuation.
Secondary:	**Secondary:**	**Secondary:**
• To describe the effect of PF-07817883 treatment versus placebo on SARS-CoV-2 RNA levels in NP samples in non-hospitalized symptomatic adult participants with COVID-19.	• Change from baseline in SARS-CoV-2 RNA level on Days 3, 10 and 14.	• E1: The estimand is the difference between the PF-07817883 dose groups and placebo in mean change from baseline in SARS-CoV-2 RNA level in NP samples in the population of non-hospitalized, symptomatic, adult participants with COVID-19 who have SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL at baseline. This analysis will exclude data after use of prohibited COVID-19 medications and after study treatment discontinuation.
• To describe the safety and tolerability of PF-07817883 relative to placebo in the treatment of non-hospitalized, symptomatic, adult participants with COVID-19.	• Incidence of treatment-emergent adverse events (TEAEs). • Incidence of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuations. • Incidence of clinically significant abnormal laboratory values, vital signs, and electrocardiograms (ECGs).	• Not applicable (NA).

Overall Design:

This is a Phase 2B, double-blind, randomized, placebo-controlled, parallel group, dose ranging study to assess the effect of PF-07817883 treatment on SARS-CoV-2 RNA level reduction in NP samples in non-hospitalized, symptomatic, adult participants with COVID-19. Approximately 228 eligible participants with a confirmed diagnosis of SARS-CoV-2 infection are planned to be randomized into the study to ensure approximately 180 participants with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL complete the study. Participants will be randomized in a 1:1:2:2 ratio to receive PF-07817883 100, 300, or 600 mg, or placebo orally every 12 hours (q12h) for 5 days (10 doses total). Study visits should take place at the investigational site.

The total study duration is up to 5 weeks and includes a screening period of no more than 48 hours before randomization, study intervention for 5 days and a 4-week follow-up period after the last administration of the study intervention.

Number of Participants:

Approximately 228 participants will be randomly assigned to study intervention to provide ~180 completers with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL.

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 before randomization. Eligible participants will receive PF-07817883 (100, 300 or 600 mg) or placebo orally q12h for 5 days. The total study duration is up to 5 weeks and includes a screening period of no more than 48 hours, study intervention for 5 days and a 4-week follow-up period after the last administration of the study intervention.

Data Monitoring Committee or Other Independent Oversight Committee: Yes

An independent internal review committee (IRC) will review unblinded data to ensure the safety of participants throughout the duration of the study, as specified in the IRC Charter. In addition to safety reviews, the IRC will review the interim analysis.

Details of the IRC are specified in the IRC Charter.

Study Population:

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

Age and Sex:

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

2. Participants ≥18 to <65 years of age at the time of the Screening Visit.

    - Woman/women of childbearing potential (WOCBP) may be enrolled.

    - All fertile participants must agree to use a highly effective method of contraception.

Disease Characteristics:

3. Confirmed SARS-CoV-2 infection as determined by rapid antigen testing (RAT) in nasal specimen collected within 48 hours prior to randomization. Investigator sites

will use test kits that are authorized for use in this study and the test result must be available to confirm eligibility.

4. 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.

Exclusion Criteria

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

1. Current need for hospitalization or anticipated need for hospitalization within 24h after randomization in the clinical opinion of the site investigator.

Medical conditions:

2. Has at least 1 characteristic or underlying medical condition (self-report is acceptable) associated with an increased risk of developing severe illness from COVID-19. The list of the characteristics or conditions includes:

   - Body mass index (BMI) ≥30 kg/m^2;
   - Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes;
   - Chronic lung disease (ie, bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension);
   - Asthma, requiring daily prescribed therapy;
   - Cardiac vascular disease, defined as history of any of the following: myocardial infarction, stroke, transient ischemic attack, heart failure, angina with prescribed nitroglycerin, coronary artery bypass graft, percutaneous coronary intervention, carotid endarterectomy, and aortic bypass;
   - Type 1 or Type 2 diabetes mellitus;
   - Chronic Kidney Disease requiring dialysis;
   - 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 (including palliative 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 [continuous positive airway pressure] [not related to COVID-19]).

3. Known medical history of active liver disease, including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or Class C, or acute liver failure.

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

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

6. Immunocompromised with ≥1 of the following:

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

    b. Receipt of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic cell transplantation (HCT) either within 2 years of transplantation or receiving immunosuppressive therapy.

    c. Moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome).

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

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

        ii. Active treatment causing significant immunosuppression, including alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, tumor necrosis factor (TNF) blockers, or other highly immunosuppressive drugs such as biologics.

    e. Hematological malignancy (including leukemia, lymphoma and myeloma) or active immunosuppressive treatment for solid tumor.

    f. Human immunodeficiency virus (HIV) infection with CD4 cell count <200 mm^3 from known medical history within the past 6 months of screening.

7. Known severe renal impairment (estimated glomerular filtration rate [eGFR] of <30 mL/min/1.73 m^2 within 6 months of the screening visit, using the serum creatinine-based chronic kidney disease epidemiology [CKD-EPI] formula).

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

    a. 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.

9. 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.

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 use of any prohibited concomitant medication(s).

12. Use of any locally available oral or injectable antiviral medication intended to treat symptomatic SARS-CoV-2 infection before and at enrollment are excluded. After enrollment, locally available SARS-CoV-2 treatment (including but not limited to molnupiravir, mAbs, outpatient IV remdesivir, convalescent plasma) will be permitted per investigator judgement. Note: PAXLOVID is contraindicated to be administered concurrently with the study intervention due to drug-drug interation (DDI) risk.

13. Expected to receive any dose of a SARS-CoV-2 vaccine within 14 days of randomization or during the study.

Prior/Concurrent Clinical Study Experience:

14. Current or previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Authorized or products with conditional approval are not considered investigational.

15. Known prior participation in this trial.

Diagnostic Assessments:

16. Laboratory assessments not required at screening unless deemed necessary by the investigator to confirm eligibility. If deemed necessary, laboratory assessments at screening will be performed at 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.

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

    - Total bilirubin (T bili) ≥2 × upper limit of normal (ULN) (except for Gilbert's syndrome)
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 × ULN
    - Absolute neutrophil count <1000/mm^3.

18. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTc corrected using Fridericia's formula [QTcF] >450 ms, complete left bundle branch block (LBBB), signs of acute myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree atrioventricular (AV) block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 ms, this interval should be rate corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

Other Exclusion Criteria:

19. Females who are pregnant or breastfeeding.

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

Study Arms and Duration:

Eligible participants for this study will be randomly assigned (1:1:2:2) to receive PF-07817883 100, 300 or 600 mg, or placebo orally q12h as specified in the table below.

Study Intervention(s)				
Intervention Name	PF-07817883	PF-07817883	PF-07817883	Placebo for PF-07817883*
Arm Name (group of participants receiving a specific treatment or no treatment)	PF-07817883 100 mg q12h	PF-07817883 300 mg q12h	PF-07817883 600 mg q12h	Placebo
Unit Dose Strength(s)	100 mg	300 mg	600 mg	0 mg
Route of Administration	Oral	Oral	oral	Oral
Use	Experimental	experimental	experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP

* 2 tablet types for placebo to match with PF-07817883 100 mg and 300 mg, respectively.
AxMP=auxiliary medicinal product; IMP=investigational medicinal product; NIMP=noninvestigational medicinal product.

Study Arm(s)				
Arm Title	PF-07817883 100 mg q12h	PF-07817883 300 mg q12h	PF-07817883 600 mg q12h	Placebo
Arm Type	Experimental	Experimental	Experimental	Placebo
Arm Description	Participants will receive PF-07817883 100 mg q12h for 5 days.	Participants will receive PF-07817883 300 mg q12h for 5 days.	Participants will receive PF-07817883 600 mg q12h for 5 days.	Participants will receive 0 mg q12h for 5 days.

Statistical Methods:

A sufficient number of participants will be screened to achieve a total of approximately 228 participants, with participants randomly assigned to PF-07817883 100, 300, 600 mg or placebo q12h in approximately a 1:1:2:2 ratio. Assuming 20% of participants will discontinue study drug treatment or have a baseline SARS-CoV-2 RNA level <4 $\log_{10}$

copies/mL, approximately 180 participants (60 in each of PF-07817883 600 mg q12h and placebo, and 30 in each of PF-07817883 100 and 300 mg q12h) with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL are expected to complete Day 5 of the study. Additional participants may be randomized to ensure 180 participants with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL who complete study drug treatment.

The sample size is based on the primary efficacy endpoint, change from baseline in SARS-CoV-2 RNA level at Day 5. CCI [redacted]

CCI [redacted]

The primary estimand is the difference between the PF-07817883 dose groups and placebo in mean change from baseline in SARS-CoV-2 RNA level in NP samples on Day 5 in the population of non-hospitalized, symptomatic, adult participants with COVID-19 who have SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL at baseline. This will exclude data after use of prohibited COVID-19 medications and after study treatment discontinuation. The primary analysis will be a Bayesian Emax model applied to the estimates from a mixed model for repeated measures (MMRM) analysis.

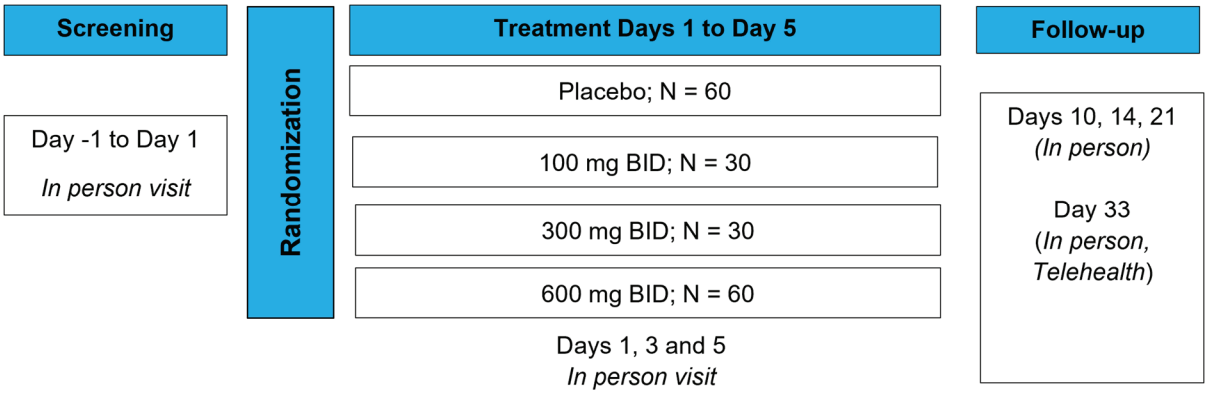
A planned formal interim analysis for virological response and safety may be performed to assess SARS-CoV-2 RNA level after approximately 50% or more participants, ie, at least 114 participants with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL, complete their study participation (including viral load assessment) through Day 5. The timing of the interim analysis is contingent on the recruitment rate.

Ethical Considerations:

This study is a placebo-controlled trial that will be conducted in participants with symptomatic COVID-19 infection who are at standard risk of progressing to severe disease, defined as <65 years of age and without underlying medical conditions associated with increased risk of developing severe illness from COVID-19 (as outlined in exclusion criterion #2). Participants enrolled may benefit from treatment with an antiviral. Although participants may be randomized to placebo, these are participants who are not expected to receive other locally available antiviral therapies outside the conduct of this trial. For this standard risk population currently there is no locally approved standard of care (SoC) treatment available; thus placebo was selected as the appropriate comparator.

The trial-specific risks and burdens for participants includes the requirement to return for follow up visits, they may experience discomforts undergoing study assessments (eg, blood samples, ECGs), and they may develop AEs due to study intervention.

1.2. Schema



N = number of completers.

1.3. Schedule of Activities

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

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

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 13	**Screen**	**Treatment Period**					**F/U**				**ET (prior to Day 33)**	**Notes:**
	Screening Day -1	**Baseline Day [1]**	**Day [2]**	**Day [3]**	**Day [4]**	**Day [5]/ EOT**	**Day [10]**	**Day [14]**	**Day [21]**	**Day [33 (28+5)] /EOS**		
Visit Window	**Day -1 to Day 1**	**0 days**	**NA**	**±1 day**	**NA**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**+5 days**	**+3 days**	Although there is a 3-day window for the Day 5 visit, sites should encourage participants to attend on Day 5 to optimize evaluation of RNA level change at Day 5.
Study Visit Location	**S**	**S**	**T**	**S**	**T**	**S**	**S**	**S**	**S**	**S/T**	**S/(T)**	• **Day 33** visit should be conducted in-person at the investigational site [S] if NP sample must be collected. • Telehealth visits [T] may be conducted in-person at the discretion of the investigator. • **ET** – if visit occurs after Day 21 may be conducted by telehealth at the discretion of the investigator.
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 8.3.1.
PHYSICAL EXAMINATION & VITAL SIGNS												
Targeted physical examination	X	X		X		X	X	X	X	X	X	• See Section 8.3.3. • Collect at Day 33 visit if participant is symptomatic.

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Visit Identifier Abbreviations used in this table may be found in Appendix 13	**Screen**	**Treatment Period**					**F/U**				**ET (prior to Day 33)**	**Notes:**
	Screening Day -1	**Baseline Day [1]**	**Day [2]**	**Day [3]**	**Day [4]**	**Day [5]/ EOT**	**Day [10]**	**Day [14]**	**Day [21]**	**Day [33 (28+5)] /EOS**		
Visit Window	**Day -1 to Day 1**	**0 days**	**NA**	**±1 day**	**NA**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**+5 days**	**+3 days**	Although there is a 3-day window for the Day 5 visit, sites should encourage participants to attend on Day 5 to optimize evaluation of RNA level change at Day 5.
Weight, height	X											• See Section 8.3.2. Height may be self-reported.
Vital signs	X	X		X		X	X	X	X	X	X	• See Section 8.3.4. • Collect at Day 33 visit if participant is symptomatic.
12-lead ECG		X		X		X	X				X	• Triplicate ECG collected at baseline prior to dosing. • Day 1 Post-dose ECGs should be performed within 30 to 90 min post-dose. • If ET visit occurs before final ECG assessment on Day 10 visit, ECG should be performed. • If Day 10 visit is missed, then ECG should be performed at Day 14. • See Section 8.3.5 for additional information.
LABORATORY ASSESSMENTS												
Safety Laboratory Assessments (Blood) – Hematology and Chemistry		X		X		X	X				X	• See Section 8.3.6 and Appendix 2. • Day 1 labs must be collected prior to first dose of study intervention. • Laboratory assessments not required at screening unless deemed necessary by the investigator to confirm eligibility. If deemed necessary, laboratory assessments at screening will be performed at local laboratory. The medical laboratory test abnormalities
Safety Laboratory Assessments (Urine) – Urinalysis		X		X		X	X				X	

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	Screening Day -1	**Baseline Day [1]**	**Day [2]**	**Day [3]**	**Day [4]**	**Day [5]/ EOT**	**Day [10]**	**Day [14]**	**Day [21]**	**Day [33 (28+5)] /EOS**		
Visit Window	**Day -1 to Day 1**	**0 days**	**NA**	**±1 day**	**NA**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**+5 days**	**+3 days**	Although there is a 3-day window for the Day 5 visit, sites should encourage participants to attend on Day 5 to optimize evaluation of RNA level change at Day 5.
Other Laboratory Assessments		X		X		X	X*				X	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. • SARS-CoV-2 serology is a part of Other Laboratory Assessment (see Appendix 2). Only Day 1 and Day 10 samples will be assessed for SARS-CoV-2 serology. *Day 10: only SARS-CoV-2 serology assessment will be done.
Pregnancy test (WOCBP only)	X									X	X	• Additional Pregnancy tests will be done whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. • See Section 8.3.7.
FSH	X											• When FSH testing is required to confirm postmenopausal status, a participant may be screened 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 8.3.7.2 and Appendix 2.
BIOMARKER ASSESSMENTS												
Rapid antigen testing	X											• Confirmed SARS-CoV-2 infection as determined by RAT using a test kit that is authorized by the sponsor in a nasal specimen collected within 2 days prior to randomization is required. • See Section 8.7.1.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 13	**Screen**	**Treatment Period**					**F/U**				**ET (prior to Day 33)**	**Notes:**
	Screening Day -1	**Baseline Day [1]**	**Day [2]**	**Day [3]**	**Day [4]**	**Day [5]/ EOT**	**Day [10]**	**Day [14]**	**Day [21]**	**Day [33 (28+5)] /EOS**		
Visit Window	**Day -1 to Day 1**	**0 days**	**NA**	**±1 day**	**NA**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**+5 days**	**+3 days**	Although there is a 3-day window for the Day 5 visit, sites should encourage participants to attend on Day 5 to optimize evaluation of RNA level change at Day 5.
SARS-CoV-2 RNA level assessment (NP)		X		X		X	X	X	X	X*	X	• See Section 8.7.5. • Day 1 NP sample should be collected prior to first dose of study intervention. • If a participant experiences symptom worsening or recurrence after completion of the 5-day treatment with study drug (ie, through Day 33), participants may subsequently attend a site for an unscheduled visit, for NP sample collection to measure SARS-CoV-2 RNA levels. *Day 33 NP sample should be collected only if participant is symptomatic at Day 21.
Specified protein research (plasma biomarkers)		X		X		X					X	• Day 1 sample should be collected prior to first dose of study intervention. • See Section 8.7.3.
Retained research sample for genetics (Prep D1)		X										• Sample collection is optional. • Prep D1 Retained Research Samples; if not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • Refer to Section 8.6.2.
Retained research samples for biomarkers (Prep B2.5, Prep R1)		X		X		X			X		X	• Sample collections are optional. • Day 1 sample should be collected prior to first dose of study intervention. • See Section 8.7.6.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 13	**Screen**	**Treatment Period**					**F/U**				**ET (prior to Day 33)**	**Notes:**
	Screening Day -1	**Baseline Day [1]**	**Day [2]**	**Day [3]**	**Day [4]**	**Day [5]/ EOT**	**Day [10]**	**Day [14]**	**Day [21]**	**Day [33 (28+5)] /EOS**		
Visit Window	**Day -1 to Day 1**	**0 days**	**NA**	**±1 day**	**NA**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**+5 days**	**+3 days**	Although there is a 3-day window for the Day 5 visit, sites should encourage participants to attend on Day 5 to optimize evaluation of RNA level change at Day 5.
PK ASSESSMENTS												
PK sample (PF-07817883)		X		X		X					X	• On Day 1 only, three blood samples for PK will be collected at 30±10, 60±15 and 90±15 minutes post-dose to remain at the site. • On Day 3, one blood sample for PK will be collected at any time during the study visit. • 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 any time during the visit, even after study intervention has been administered. • Refer to Section 8.5.
Sample for blood to plasma ratio		X										• Blood to plasma ratio sample will be collected at 60±15 minutes post-dose. Do NOT centrifuge.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 13	**Screen**	**Treatment Period**					**F/U**				**ET (prior to Day 33)**	**Notes:**
	Screening Day -1	**Baseline Day [1]**	**Day [2]**	**Day [3]**	**Day [4]**	**Day [5]/ EOT**	**Day [10]**	**Day [14]**	**Day [21]**	**Day [33 (28+5)] /EOS**		
Visit Window	**Day -1 to Day 1**	**0 days**	**NA**	**±1 day**	**NA**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**+5 days**	**+3 days**	Although there is a 3-day window for the Day 5 visit, sites should encourage participants to attend on Day 5 to optimize evaluation of RNA level change at Day 5.
PK micro-sampling (PF-07817883)		X	X		X							• PK micro-sample(s) will be collected by Tasso micro-sampling device on Day 1, 60±10 min post-dose simultaneously with the PK sample draw. • A Tasso micro-sample will be self-collected at home before administration of the second dose. This can occur on Day 1 evening if first dose is taken in the morning or on Day 2 morning if first dose is taken in the evening on Day 1. • Self-collected at home by Tasso micro-sampling device at the following timepoints: • Day 2 before the evening dose, • Day 4 after the morning dose at the following times: 1 sample between 30 to 90 minutes, 1 sample between 2 to 6 hours, and 1 sample 8 to 12 hours after the dose (the last sample should be collected before the evening dose). • Tasso micro-sampling can occur regardless of whether this coincides with a site visit. • Refer to Section 8.5.
RANDOMIZATION												
Randomization		X										• At randomization, the participant enrollment number and dose level allocation are assigned.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 13	**Screen**	**Treatment Period**					**F/U**				**ET (prior to Day 33)**	**Notes:**
	Screening Day -1	**Baseline Day [1]**	**Day [2]**	**Day [3]**	**Day [4]**	**Day [5]/ EOT**	**Day [10]**	**Day [14]**	**Day [21]**	**Day [33 (28+5)] /EOS**		
Visit Window	**Day -1 to Day 1**	**0 days**	**NA**	**±1 day**	**NA**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**+5 days**	**+3 days**	Although there is a 3-day window for the Day 5 visit, sites should encourage participants to attend on Day 5 to optimize evaluation of RNA level change at Day 5.
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 (total 10 doses). • All subsequent doses may be self-administered outside the study clinic (eg, at home). • See Section 6.1 for additional information.
CONCOMITANT TREATMENT(S)												
Prior/concomitant medication(s)	X	X		X		X	X	X	X	X	X	• See Section 6.9.
Adjunctive therapeutic procedures	X	X		X		X	X	X	X	X	X	• Will be collected through the Day 33 visit. • Please see Section 8.3.8.
STUDY PROCEDURES& ASSESSMENTS												
Collect/update secondary contacts		X					X		X			• See Section 8.1.1.
Record supplemental oxygen requirements	X	X		X		X	X	X	X	X	X	• See Section 8.2.4.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 13	**Screen**	**Treatment Period**					**F/U**				**ET (prior to Day 33)**	**Notes:**
	Screening Day -1	**Baseline Day [1]**	**Day [2]**	**Day [3]**	**Day [4]**	**Day [5]/ EOT**	**Day [10]**	**Day [14]**	**Day [21]**	**Day [33 (28+5)] /EOS**		
Visit Window	**Day -1 to Day 1**	**0 days**	**NA**	**±1 day**	**NA**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**+5 days**	**+3 days**	Although there is a 3-day window for the Day 5 visit, sites should encourage participants to attend on Day 5 to optimize evaluation of RNA level change at Day 5.
Participant-completed study diary (revised COVID-19 signs and symptoms, and global impression questions)		Every day from Day 1 through Day 29										• Revised COVID-19 signs and symptom eDiary assessments should be completed pre-dose, prior to other study procedures such as ECG recordings and laboratory assessments. • See Section 8.2.1 and Section 8.2.5.
Staff review of study diary						X	X	X	X	X	X	• See Section 8.2.1.
Participant-completed study intervention log		Day 1 through Day 5										• Study intervention log should be completed daily on Day 1 through Day 6 if only 1 dose was administered on Day 1. • See Section 6.5.
Record COVID-19-related medical visits				X		X	X	X	X	X	X	• COVID-19-related medical visits a participant has attended since the last assessment will be collected. • See Section 8.2.2.
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 6.5.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 13	**Screen**	**Treatment Period**					**F/U**				**ET (prior to Day 33)**	**Notes:**
	Screening Day -1	**Baseline Day [1]**	**Day [2]**	**Day [3]**	**Day [4]**	**Day [5]/ EOT**	**Day [10]**	**Day [14]**	**Day [21]**	**Day [33 (28+5)] /EOS**		
Visit Window	**Day -1 to Day 1**	**0 days**	**NA**	**±1 day**	**NA**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**+5 days**	**+3 days**	Although there is a 3-day window for the Day 5 visit, sites should encourage participants to attend on Day 5 to optimize evaluation of RNA level change at Day 5.
Study intervention accountability			X	X	X	X	X				X [if needed]	• Study intervention accountability is also performed at the Day 10 visit if the participant administered treatment after the Day 5 visit was conducted. • Study intervention accountability check at Day 2 and Day 4 will be an optional phone call. • See Section 6.5.
Contraception check	X	X		X		X	X	X	X	X	X	• See Section 5.3.1.
Vital status check										X	X	• Verify mortality status of participants, if needed. • See Section 8.1.1.
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X	X	X	• AEs should be assessed by means of a telehealth visit if not possible via an in-person visit. • See Section 8.4 for additional information.

2. INTRODUCTION

PF-07817883 is a potent and selective inhibitor of the SARS-CoV-2 M^{pro}, that is being developed as an oral treatment in patients with COVID-19.

2.1. Study Rationale

The purpose of this study is to assess the effect of PF-07817883 on SARS-CoV-2 RNA level reduction in NP samples and to evaluate the safety of PF-07817883 treatment in non-hospitalized, symptomatic, adult participants with COVID-19. The study is designed as a dose-ranging study to collect pharmacological and safety information to inform dose selection of PF-07817883 in later stage Phase 2/3 studies.

2.2. Background

In December 2019, COVID-19 was identified as a new, potentially fatal, respiratory infection caused by the novel coronavirus, SARS-CoV-2. The WHO declared COVID-19 a Public Health Emergency of International Concern on 20 January 2020 and further characterized the disease outbreak as a pandemic on 11 March 2020.[1]

COVID-19 manifests as a wide range of illnesses, from asymptomatic infection to severe pneumonia, ARDS, and death. While the majority of cases (approximately 80%) are asymptomatic or mild,[2] patients who are hospitalized with COVID-19 may have significant morbidity and mortality,[3,4] and are at increased risk of developing complications such as ARDS, acute cardiac injury, thromboembolic events and/or kidney injury.[5-7] Moreover, other comorbidities, such as hypertension, obesity, and diabetes, as well as older age and male sex increase the risk for worse outcomes.[8,9]

The coronavirus M^{pro} 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). Mutagenesis experiments with other coronaviruses and picornaviruses that are related to SARS-CoV-2 (picornavirus-like supercluster) have demonstrated that the activity of the M^{pro} is essential for viral replication. No close human analogs of coronavirus M^{pro} enzymes are known, suggesting that appropriate M^{pro} inhibitors may function as selective inhibitors of SARS-CoV-2 and other coronaviruses as therapeutic agents.

Inhibition of the SARS-CoV-2 M^{pro} by PAXLOVID has demonstrated the efficacy of an antiviral in the reduction in hospitalization and death in mild-to-moderate COVID-19 patients with high risk of progression to severe disease. But some high-risk patients may be ineligible for PAXLOVID due to DDIs. Hence, there remains an important need for additional safe and more effective therapeutic interventions.

2.2.1. Nonclinical Studies of PF-07817883

Data from nonclinical studies support the planned clinical trials with PF-07817883; these studies are described in the IB.

PF-07817883 exhibits broad spectrum inhibitory activity across the Coronaviridae family of M^{pro} enzymes.

In vitro, the antiviral activity of PF-07817883 against SARS-CoV-2 was evaluated in several cell lines. In all cellular systems tested, PF-07817883 demonstrates potent antiviral activity against SARS-CoV-2. In dNHBE cells, a physiologically relevant, primary human lung alveolar epithelial cell line, PF-07817883 inhibited SARS-CoV-2 viral replication with an EC_{50} of CCI µM and EC_{90} of CCI µM after 3 days of drug exposure. PF-07817883 also exhibited antiviral efficacy against SARS-CoV-1, HCoV-229E, and MERS-CoV in cellular systems. In addition, PF-07817883 demonstrated antiviral activities against Alpha, Beta, Delta, Gamma, Lambda, Mu, and Omicron variants in the Vero TMPRSS2 and VeroE6 P-gp KO cells.

In accordance with FDA and EMA DDI guidance, CCI

The toxicity of PF-07817883 was evaluated in CCI There were no adverse findings in any of the studies. From a preliminary population PK model based on FIH data, the total C_{max} and AUC_{24} for 600 mg BID CCI , respectively. The NOAELs in the CCI studies CCI over the human unbound C_{max} and AUC_{24} at a dose of 600 mg BID.

CCI

More details are presented in the IB.

2.2.2. Clinical Overview

C5091001 is the first clinical study using PF-07817883. It is a six-part study. PART-1 is a SAD study, PART-2 is a MAD study, PART-3 is a rBA/FE study, PART 4 is a ME study, PART-5 is a DDI study and PART-6 is a SE study.

PART-1 included 2 interleaving cohorts with a total of 16 participants with 3-period cross-over in each cohort. For each period, up to 6 participants received a single oral dose of PF-07817883 and up to 2 participants received placebo. Single doses of PF-07817883 ranged from 150 mg to 4000 mg. CCI in Cohort 1 were CCI and Other CCI

CCI [redacted]

PART-2 included 3 cohorts evaluating safety, tolerability, and PK data at 200 mg, 600 mg, and 1500 mg doses of PF-07817883 or placebo administered BID for up to 10 days. As of 18 January 2023, 18 participants were randomized in 3 cohorts in PART-2. CCI [redacted] in Cohort 4 (PF-07817883 600 mg BID or placebo) of PART-2 due to Other (CCI [redacted]).

PART-4 included a single cohort of 6 male participants to evaluate the metabolism and excretion of a single dose of PF-07817883 600 mg. Cohort 11 of PART-5 included 14 participants and evaluated the effect of steady state PF-07817883 600 mg on PK of midazolam in healthy participants.

2.2.2.1. Safety Overview

The preliminary data collected (data snapshot 18 January 2023) in PART-1, PART-2, and (data snapshot 06 February 2023) in PART-4 and PART-5 (Cohort 11) of the Phase 1 study (C5091001) demonstrated an acceptable safety profile at single doses of PF-07817883 or placebo ranging from 150 mg to 4000 mg in PART-1, doses of 200 mg to 1500 mg BID of PF-07817883 or placebo for 10 days in PART-2, and 600 mg BID in PART-4 and PART-5. Dose escalation stopping rules were not triggered and MTD was not achieved. There have been no deaths, SAEs or SUSARs reported. CCI [redacted]

[redacted] There were no obvious trends in, or association of, TEAEs with dose level of PF-07817883 in PART-1, PART-2, PART-4, or PART-5 (Cohort 11); however, the small numbers of participants studied at each dose level do not permit any definitive conclusions about the relationship between dose and tolerability.

Further details on the clinical safety of PF-07817883 are provided in the current IB.

2.2.2.2. Summary of PF-07817883 Pharmacokinetics in Humans

CCI [redacted]

CCI

[redacted]

CCI

Further details on the clinical PK of PF-07817883 are provided in the current IB.

2.3. Benefit/Risk Assessment

The purpose of the study is to generate safety, tolerability and PK data for further clinical development of PF-07817883 as a potential new, pharmacological agent for the treatment of COVID-19. PF-07817883 has been evaluated in non-clinical studies and in an ongoing study (C5091001) in healthy adult participants.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07817883 may be found in the Investigator's Brochure, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07817883		
CCI		

2.3.2. Benefit Assessment

PF-07817883 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. The PF-08717883 doses administered in this study are expected to have clinically relevant antiviral effects. On this basis, the potential benefit to individual study participants who receive the study intervention may include a shorter time to clinical recovery, prevention of hospitalization, and a lower probability of progressing to more severe illness or death. The potential benefit of the study is that it may provide a new treatment option for non-hospitalized patients with COVID-19 who are at standard 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 ongoing COVID-19 global pandemic, the continued high mortality and morbidity burden, the potential for future epidemic outbreaks, the limited outpatient treatment options available and the measures taken to minimize risk to participants in this study, the potential risks identified in association with PF-07817883 are justified by the anticipated benefits that may be afforded to participants with COVID-19. The participants enrolled into this study will include those at standard risk of progression to severe disease, and so the benefit for this population may be considered modest. However, this study will provide information needed to that will help determine the correct dose to use in high-risk populations. An independent IRC 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 IRC Charter.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To describe the effect of PF-07817883 treatment versus placebo on SARS-CoV-2 RNA levels in NP samples in non-hospitalized symptomatic adult participants with COVID-19.	• Change from baseline in SARS-CoV-2 RNA level on Day 5.	• E1: The estimand is the difference between the PF-07817883 dose groups and placebo in mean change from baseline in SARS-CoV-2 RNA level in NP samples in the population of non-hospitalized, symptomatic, adult participants with COVID-19 who have SARS-CoV-2 RNA level ≥ 4 $\log_{10}$ copies/mL at baseline. This analysis will exclude data after use of prohibited COVID-19 medications and after study treatment discontinuation.
Secondary:	**Secondary:**	**Secondary:**
• To describe the effect of PF-07817883 treatment versus placebo on SARS-CoV-2 RNA levels in NP samples in non-	• Change from baseline in SARS-CoV-2 RNA level on Days 3, 10, and 14.	• E1: The estimand is the difference between the PF-07817883 dose groups and placebo in mean change from baseline in SARS-CoV-2 RNA level in NP samples in the population of non-

Objectives	Endpoints	Estimands
hospitalized symptomatic adult participants with COVID-19.		hospitalized, symptomatic, adult participants with COVID-19 who have SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL at baseline. This analysis will exclude data after use of prohibited COVID-19 medications and after study treatment discontinuation.
• To describe the safety and tolerability of PF-07817883 relative to placebo in the treatment of non-hospitalized, symptomatic, adult participants with COVID-19.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations. • Incidence of clinically significant abnormal laboratory values, vital signs, and ECGs.	• NA
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To assess the effect of PF-07817883 treatment on the duration and severity of signs and symptoms in non-hospitalized, symptomatic, adult participants with COVID-19.	• Proportion of participants with any targeted signs and symptoms attributed to COVID-19 over time . • Proportion of participants with any targeted severe sign or symptom attributed to COVID-19 over time. • Number of participants with sustained alleviation of all targeted signs/symptoms over time. • Number of participants with sustained resolution of all targeted signs and symptoms over time. • Duration of targeted COVID-19 sign or symptom. • Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms over time. • Proportion of participants with symptom rebound at Day 10, 14, and 21.	• NA
• To assess the effect of PF-07817883 treatment on COVID-19-related medical visits, hospitalization or death and all-cause mortality in non-hospitalized, symptomatic, adult participants with COVID-19.	• Proportion of participants with COVID-19 related medical visits or hospitalization, over time. • Proportion of participants with death (all cause) over time. • Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization over time.	• NA
• To determine the PK of PF-07817883 in non-hospitalized, symptomatic, adult participants with COVID-19.	• PF-07817883 PK in plasma and whole blood (if feasible).	• NA
• To describe the effect of PF-07817883 treatment versus placebo on SARS-CoV-2 RNA levels in NP samples in non-	• Change from Day 5 in SARS-CoV-2 RNA level at Days 10, 14 and 21. • Change from baseline in SARS-CoV-2 RNA levels at Days 21 and 33.	• NA

Objectives	Endpoints	Estimands
hospitalized symptomatic adult participants with COVID-19.	• Proportion of participants with SARS-CoV-2 RNA level <LLOQ in NP samples over time. • Proportion of participants with viral rebound at Day 10, Day 14, or Day 21.	
• To describe the effect of PF-07817883 treatment on infectivity of SARS-CoV-2 collected from NP samples.	• Change from baseline in SARS-CoV-2 infectious titer on Days 3, 5, 10 and 14, and Days 21 and 33 (if data permit).	• NA

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2B, double-blind, randomized, placebo-controlled, parallel group, dose ranging study to assess the effect of PF-07817883 treatment on SARS-CoV-2 RNA level reduction in NP samples in non-hospitalized, symptomatic, adult participants with COVID-19. Approximately 228 eligible participants with a confirmed diagnosis of SARS-CoV-2 infection are planned to be randomized into the study to ensure approximately 180 participants with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL complete the study drug treatment. Participants will be randomized in a 1:1:2:2 ratio to receive PF-07817883 100, 300, or 600 mg, or placebo orally q12h for 5 days (10 doses total). Study visits should take place at the investigational site.

The total study duration is up to 5 weeks and includes a screening period of no more than 48 hours before randomization, study intervention for 5 days and a 4-week follow-up period after the last administration of the study intervention.

An independent IRC will review unblinded data to ensure the safety of participants throughout the duration of the study, as specified in the IRC Charter. In addition to safety reviews, the IRC will review the following:

- A planned formal interim analysis for virological response and safety may be performed to assess SARS-CoV-2 RNA level after approximately 50% or more participants, ie, at least 114 participants with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL, complete their study participation (including viral load assessment) through Day 5. The timing of the interim analysis will be contingent on the recruitment rate.

Subsequent to the planned interim analysis, there will be 1 planned analysis for reporting the results of this study. The primary analysis will be performed after all participants have completed the Day 33 visit.

4.2. Scientific Rationale for Study Design

This study evaluates the safety and the potential effect of an investigational agent on reducing SARS-CoV-2 viral RNA level. The study is designed as a dose-ranging study to

collect pharmacological activity and safety information to facilitate dose selection for later stage studies.

Although mAbs and antivirals have since become available there remains an important need to develop therapeutics for the treatment of COVID-19 infection. Several mAbs became available under EUA for the treatment of mild-to-moderate COVID-19 infection in select populations. However, mAbs such as bamlanivimab with etesivimab, sotrovimab, and more recently bebtelovimab have since been removed as treatment options due to diminished efficacy with the emergence of SARS-CoV-2 variants.[10,11] Antivirals such as PAXLOVID and remdesivir IV are available and considered preferred therapy for non-hospitalized adults, while molnupiravir is considered an alternative therapy by the COVID-19 Treatment Guidelines Panel.[11] However, these therapeutics are limited to outpatient populations with mild-to-moderate COVID-19 infection at risk for progressing to severe disease. Furthermore, some high-risk patients may be ineligible for PAXLOVID due to DDIs, and remdesivir may be inaccessible for some patients as it requires administration in a health care setting and returning for 3 subsequent days for daily IV dosing.

Despite these advances, there remains an important need for additional safe and more effective therapeutic interventions that do not require administration in a healthcare setting, are not limited by DDIs, and with a risk/benefit profile supportive of administration to a broader patient population. The direct reduction of viral replication, through inhibition of other critical viral enzymes, offers an important mechanism as monotherapy or in combination, to achieve greater patient benefit.

Efficacy assessments (including participant reported COVID-19-related symptoms and severity, and COVID-19-related medical visits) will be collected through Day 33. 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 samples will be collected at specified timepoints to assess SARS-CoV-2 RNA level 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 since as of this date there is no globally approved SoC treatment for this patient population. Participants in either treatment group may receive SoC therapy so long as it is not prohibited under Section 5.1 or Appendix 9.

4.2.1. Diversity of Study Population

Diversity of study population in this protocol applies to sites in the US only. The diversity strategy will include sites with the potential to support the recruitment of diverse populations. 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-07817883 in clinical practice. The following strategies may be explored in support of diverse recruitment efforts:

- Selecting sites that have access to diverse participants within their locale.

- Creating and completing individual site recruitment plans in collaboration with sites.
- Have proactive discussions with investigator sites throughout the enrollment period to assess and reevaluate site specific strategies as needed to best position each site for the most diverse representation enrollment outcomes.
- Developing recruitment and retention materials with culturally and linguistically appropriate language and imagery to resonate with underrepresented populations.
- Translating all patient-facing materials into US Spanish.
- Providing investigators with recruitment materials for both potential participants and other HCPs.
- Educating site staff on the importance of including diverse participants.
- Monitor diverse enrollment to identify potential opportunities to include diverse populations.

4.2.2. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of PF-07817883 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

The dosing regimens to be evaluated in this study are placebo, 100, 300 and 600 mg PF-07817883 q12h administered orally for 5 days. 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 ongoing Phase 1 study (C5091001), and in vitro pharmacology studies with PF-07817883.

A preliminary population PK model was developed using PK data (unaudited) from the single ascending dose and multiple ascending dose parts of the Phase 1 study (C5091001). Following the first dose of 100, 300 and 600 mg of PF-07817883 q12h, median unbound (total) C_{trough} of PF-07817883 are predicted to be approximately 43 (92), 119 (253) and 226 (482) ng/mL, ie, approximately 1.3, 3.5 and 6.6-fold higher than the in vitro EC_{90} (total) of CCI ng/mL determined in dNHBE cells (equivalent to free in vitro EC_{90} of 70 nM, fu, human=CCI), respectively. As the majority of antivirals are administered to maintain concentrations either at or above the EC_{90}, lower doses below 100 mg are not planned for this

study. At the selected dose levels of 100, 300 and 600 mg q12h, for a hypothetical inter-subject variability of 60%, more than 63, 96 and 99% of the participants, respectively, are predicted to maintain free PF-07817883 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 including PAXLOVID, molnupiravir and remdesivir in the treatment of COVID-19.

Preliminary safety data from study C5091001, collected up to 22 December 2022, showed an acceptable safety profile for single doses of PF-07817883 ranging from 150 mg to 4000 mg and for 10-day repeated doses ranging from 200 mg BID to 1500 mg BID.

The proposed dosing regimen of 100, 300 and 600 mg of PF-07817883 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 they have 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. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

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

2. Participants ≥18 to <65 years of age 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.

Disease Characteristics:

3. Confirmed SARS-CoV-2 infection as determined by RAT in nasal specimen collected within 48 hours prior to randomization. Investigator sites will use test kits that are authorized for use in this study and the test result must be available to confirm eligibility.

4. 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 10 for criteria).

5.2. Exclusion Criteria

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

1. Current need for hospitalization or anticipated need for hospitalization within 24h after randomization in the clinical opinion of the site investigator.

Medical conditions:

2. Has at least 1 characteristic or underlying medical condition (self-report is acceptable) associated with an increased risk of developing severe illness from COVID-19. The list of the characteristics or conditions includes:

   - BMI $\geq$30 kg/m^2;

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

   - Chronic lung disease (ie, bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension);

   - Asthma, requiring daily prescribed therapy;

   - Cardiac vascular disease, defined as history of any of the following: myocardial infarction, stroke, transient ischemic attack, heart failure, angina with prescribed nitroglycerin, coronary artery bypass graft, percutaneous coronary intervention, carotid endarterectomy, and aortic bypass;

   - Type 1 or Type 2 diabetes mellitus;

- Chronic Kidney Disease requiring dialysis;
- 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 (including palliative 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]).

3. Known medical history of active liver disease, including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or Class C, or acute liver failure.

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

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

6. Immunocompromised with ≥1 of the following:

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

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

    c. Moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome).

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

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

        ii. Active treatment causing significant immunosuppression, including alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, TNF blockers, or other highly immunosuppressive drugs such as biologics.

    e. Hematological malignancy (including leukemia, lymphoma and myeloma) or active immunosuppressive treatment for solid tumor.

f. HIV infection with CD4 cell count <200 mm^3 from known medical history within the past 6 months of screening.

7. Known severe renal impairment (eGFR of <30 mL/min/1.73 m^2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula[12]).

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

   a. 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.

9. 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.

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 use of any prohibited concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

12. Use of any locally available oral or injectable antiviral medication intended to treat symptomatic SARS-CoV-2 infection before and at enrollment are excluded. After enrollment, locally available SARS-CoV-2 treatment (including but not limited to molnupiravir, mAbs, outpatient IV remdesivir, convalescent plasma) will be permitted per investigator judgement. Note: PAXLOVID is contraindicated to be administered concurrently with the study intervention due to DDI risk (refer to Section 6.9).

13. Expected to receive any dose of a SARS-CoV-2 vaccine within 14 days of randomization or during the study.

Prior/Concurrent Clinical Study Experience:

14. Current or previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Authorized or products with conditional approval are not considered investigational.

15. Known prior participation in this trial.

Diagnostic Assessments:

16. Laboratory assessments not required at screening unless deemed necessary by the investigator to confirm eligibility. If deemed necessary, laboratory assessments at screening will be performed at 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.

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

    - T bili ≥2 × ULN (except for Gilbert's syndrome)
    - AST or ALT ≥2.5 × ULN
    - Abs neutrophil count <1000/mm^3.

18. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of acute myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 ms, this interval should be rate corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

Other Exclusion Criteria:

19. Females who are pregnant or breastfeeding.

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

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and 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 and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

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

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to PF-07817883 100 mg, 300 mg and 600 mg (2 x 300 mg) or matching placebo tablets.

6.1. Study Intervention(s) Administered

Study Intervention(s)				
Intervention Name	PF-07817883	PF-07817883	PF-07817883	Placebo for PF-07817883
Arm Name (group of participants receiving a specific treatment or no treatment)	PF-07817883 100 mg q12h	PF-07817883 300 mg q12h	PF-07817883 600 mg q12h	Placebo
Type	Drug	Drug	Drug	Placebo

Study Intervention(s)				
Dose Formulation	Tablet	Tablet	Tablet	Tablet*
Unit Dose Strength(s)	100 mg	300 mg	300 mg	0 mg
Dosage Level(s)	100 mg q12h for 5 days	300 mg q12h for 5 days	600 mg q12h for 5 days	0 mg q12h for 5 days
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IPM.	Provided centrally by the sponsor. Refer to the IPM.	Provided centrally by the sponsor. Refer to the IPM.	Provided centrally by the sponsor. Refer to the IPM.
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement. Products will be provided with blinded labels.	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement. Products will be provided with blinded labels.	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement. Products will be provided with blinded labels.	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement. Products will be provided with blinded labels.
Current/ Former Name(s) or Alias(es)	PF-07817883	PF-07817883	PF-07817883	NA

* 2 tablet types for placebo to match with PF-07817883 100 mg and 300 mg, respectively.

Study Arm(s)				
Arm Title	PF-07817883 100 mg	PF-07817883 300 mg	PF-07817883 600 mg	Placebo
Arm Type	Experimental	Experimental	Experimental	Placebo
Arm Description	Participants will receive PF-07817883 100 mg q12h from Day 1 through Day 5.	Participants will receive PF-07817883 300 mg q12h from Day 1 through Day 5.	Participants will receive PF-07817883 600 mg q12h from Day 1 through Day 5.	Participants will receive placebo 0 mg q12h from Day 1 through Day 5.
Associated Intervention Labels	PF-07817883 (100 mg q12h)	PF-07817883 (300 mg q12h)	PF-07817883 (600 mg q12h)	Placebo q12h

6.1.1. Administration

PF-07817883 100 mg, 300 mg and 600 mg or matching placebo tablets will be taken every 12 hours for 5 days. Participants will be dispensed 3 bottles on Day 1 and should take 1 tablet from each bottle every 12 hours. All three tablets should be taken within 5 minutes. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

Participants are required take the first dose of study intervention on Day 1, during the in-person visit. All subsequent doses may be self-administered outside the study clinic (eg, at home). The study intervention should be taken every 12 hours (±4 hours), and not more than twice in a calendar day. Depending on the time of first dose, the timing of the second dose may be adjusted slightly to allow the participant/caregiver to select a convenient 12 hour dosing schedule as long as the next dose is taken at least 4 hours, but no later than 16 hours, after the first dose. Once the dosing schedule is adjusted, all subsequent doses should be taken every 12 hours (±4 hours).

Participants may take the study intervention with or without food. Refer to the IPM 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 that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

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

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

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be

quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

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

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

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

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

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

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using unique container numbers via an IRT system in the bottles 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 bottles provided throughout the course of dosing.

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. Assignment to Study Intervention

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

study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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

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

Returned study intervention must not be redispensed to the study participants.

6.4. Blinding

This is a double-blind study.

6.4.1. Blinding of Participants

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

6.4.2. Blinding of Site Personnel

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

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

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

6.4.3. Blinding of the Sponsor

Sponsor staff will be blinded to participants' assigned study intervention, except for sponsor staff involved in the assignment or distribution of study intervention. Sponsor staff who are not directly involved with the conduct of this study will prepare analyses and documentation containing unblinded data while the study is ongoing to support interactions with the IRC. The study will be unblinded after all participants complete the Day 33 visit (or ET prior to Day 33 visit) and analyses through Day 33, including the primary efficacy endpoint analyses, will be conducted. Details of the timing of unblinding will be outlined in the Unblinding Plan.

6.4.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management

of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

6.5. Study Intervention Compliance

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

Site personnel will review the participant-completed dosing diary at in person visits (Day 3 and Day 5) and during an (optional) phone call on Day 2 and Day 4, during the study intervention period, preferably after the participant has self-administered the morning dose of the study intervention. If any noncompliance with dosing is suspected, site personnel will remind the participant of the relevant study procedures and/or entering the information in the diary as applicable.

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

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets/capsules during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the number of PF-07817883 tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

The following noncompliance cases will be considered medication errors (see Section 8.4.10).

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

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

6.6. Dose Modification

Dose modification for PF-07817883 is not allowed.

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

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

6.8. Treatment of Overdose

For this study, a dose of >12 tablets of "PF-07817883 300 mg or placebo" or >36 tablets of "PF-07817883 100 mg or placebo", or any combination of these tablets achieving maximum nominal dose of CCI mg within a 24-hour time period, will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

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

6.9. Prior and Concomitant Therapy

Prior Therapy

Use of an antiviral or mAb therapy for the treatment of COVID-19 within 30 days or 5 half-lives (whichever is longer) prior to screening is prohibited.

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

All prescription and over-the-counter medications including vaccines taken by the participant within 30 days before study entry (considered prior treatment) will be recorded. Concomitant therapies will be collected through the Day 33 visit.

Permitted During the Study

All participants may receive supportive therapy for COVID-19, in addition to study intervention, unless listed as prohibited medication (see Appendix 9) or as defined in Section 5.2. Supportive therapy for symptom management may include antipyretics, analgesics, antitussives and anti-emetics.

All participants may receive locally available mAb treatment, direct-acting antiviral treatment for SARS-CoV-2 (eg, remdesivir, molnupiravir), or convalescent COVID-19 plasma treatment for COVID-19 during the study period after enrollment per investigator judgement. If the participant needs to receive a direct-acting SARS-CoV-2 antiviral during drug dosing period, study drug (PF-07817883 or placebo) should be discontinued (refer to Section 7.1).

Prohibited During the Study

If participants require treatment with another antiviral as part of SoC, they will be able to do so, with the exception of PAXLOVID which is contraindicated to be administered concurrently with the study intervention due to DDI risk. The concomitant use of PAXLOVID is not permitted due to overlapping MOA and the ritonavir component may increase plasma concentrations of PF-07817883. If the participant needs to receive a direct-acting SARS-CoV-2 antiviral during drug dosing period, study drug (PF-07817883 or placebo) should be discontinued (refer to Section 7.1). COVID-19 vaccinations are permitted after the Day 33 visit.

PF-07817883 is primarily metabolized by CYP3A4. Therefore, concomitant use of any medications or substances that are moderate to strong inducers or inhibitors of CYP3A4 are prohibited within 28 days or 5 half-lives (whichever is longer) prior to dosing of study intervention and during study treatment.

A non-exhaustive list of prohibited and precautionary medications is provided in Appendix 9.

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 before the first dose of study intervention is administered to determine if they are strong inducers of CYP3A4 and thus should be prohibited.

6.9.1. 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.
- If post-screening eGFR is <30 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.
- Receipt of locally available concomitant, non-prohibited, direct-acting antiviral therapy for SARS-CoV-2.

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

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for all subsequent scheduled assessments. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

7.1.1. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR or eCrCL require expedited evaluation to differentiate AKI from DICI. DICI is defined as transporter-mediated effect related to altered renal tubular creatinine handling without histological injury.

Differentiating Acute Kidney Injury from DICI:

AKI may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI and from DICI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.

Both AKI (including DIKI) and DICI are associated with (i) confirmed Screat increase ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR (ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Only AKI (including DIKI) is associated with

- (i) simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase OR (ii) confirmed albuminuria increase (see Appendix 7 for Grades A1 to A3 quantitation) OR (iii) urine volume <0.5 mL/kg/h for 6 consecutive hours.
- AKI is associated with decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available).

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either there is (i) new-onset or worsening albuminuria or proteinuria are detected or (ii) urine volume (if measured) is <0.5 mL/kg/h for 6 consecutive hours.

Only DICI is associated with:

- Confirmed Screat increase without confirmed increase in reflex Scys AND confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results. Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals. If appropriate, nephrology consultation may be recommended to facilitate differentiation of renal parenchymal disease, pre-renal azotemia, and post-renal obstruction. All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

7.1.2. Liver Injury

Please refer to Appendix 6 for suggested actions and follow-up assessments.

7.1.3. ECG Changes

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

- QTcF >500 ms;
- Change from baseline: QTcF >60 ms and QTcF > 450 ms.

Please refer to Section 8.3.5 for suggested actions and follow up assessments. If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

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

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

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

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

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

Procedures conducted as part of the participant's routine clinical management (eg, 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 make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

The total blood sampling volume for individual participants in this study is approximately 240 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

8.1.1. Secondary Contacts

The investigator will collect contact information for at least 2 individuals who can be contacted if the participant cannot be reached after multiple attempts (repeat/update as

needed) at the times indicated on the SoA. Secondary contacts may be used to determine if a participant is lost to follow-up and/or vital status check (whether the participant is alive or dead).

8.1.2. Telehealth Visits

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

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Confirm the participant has completed the COVID-19 signs and symptoms eDiary assessments.

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

Day 33 and ET visits may be conducted by telehealth as outlined in the SoA, and if needed may be conducted in person at the discretion of the investigator. If a NP sample needs to be collected on Day 33, this must be an in person visit at the site. If ET occurs prior to Day 21, this visit must also be an in person visit.

8.2. Efficacy Assessments

8.2.1. Participant Diary

Participants will be provided an electronic handheld device or will use their own device to record daily COVID-19 signs and symptoms, and other 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, 24 hours), thus providing an accurate representation of the participant's experience at

that time. The participant is able to make revisions to incorrect entries before pressing the save or submit button. In the event that a participant becomes aware of an error in data after the entry is saved, a change to the diary data may only be made by the investigator submitting a data clarification form. Data reported in the participant diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the sponsor or delegate at all times via an internet-based portal.

8.2.2. COVID-19-Related Medical Visit Details

Details of participants' COVID-19-related medical visits (ie, hospitalization, practitioner's office, home healthcare services, telemedicine, urgent care, emergency room ≤24 hours, extended care facility stay) will be collected during study visits, including level of care (eg, ICU status), dates of utilization, and admission and discharge dates, as applicable. Whether medical visits are considered COVID-19-related will be determined by the investigator, for all outpatient and inpatients visits.

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.

8.2.3. 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 8.2.1.

COVID-19-related symptoms will be evaluated in accordance with FDA guidelines (Appendix 10).[13] 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.

Five additional COVID-19 daily symptom diary items are included in the revised study diary: 1) Shortness of breath (difficulty breathing) while resting, 2) Shortness of breath (difficulty breathing) while physically active*, 3) Chest pain, 4) Low energy or tiredness after physical activity*, and 5) Difficulty concentrating. The response options for these questions are: None = 0, Mild = 1, Moderate = 2, or Severe = 3, and *I did not perform physical activity = 0 where applicable.

8.2.4. Oxygen Support Details

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

8.2.5. 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:[13]

- In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)? Yes or No.
- In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)? Yes or No.
- In the past 24 hours, what was the severity of your overall COVID-19-related symptoms at their worst? None, Mild, Moderate, or Severe.

The following three anchor items will also be included in the ePRO:

- Fatigue:

  Please choose the response below that best describes the severity of your physical fatigue (ie, weakness, tiredness, lack of energy) over the past 7 days: None, Mild, Moderate, Severe or Very severe.

- Shortness of Breath:

  Please choose the response below that best describes the severity of your shortness of breath (difficulty breathing) over the past 7 days: None, Mild, Moderate, Severe or Very severe.

- Cognitive Function:

  Please choose the response below that best describes the severity of your difficulty concentrating over the past 7 days: None, Mild, Moderate, Severe or Very severe.

8.3. Safety Assessments

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

8.3.1. 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. All COVID-19 vaccinations received at any time prior to the planned first dose will also be collected.

8.3.2. Height and Weight

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

8.3.3. Targeted Physical Examinations

Physical examinations to be completed before administration of study intervention.

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 8.4.1 to 8.4.3.

8.3.4. Vital Signs

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

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

Blood pressure and PR 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 PR 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.

8.3.4.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with the participant, preferably 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.

8.3.4.2. Temperature and Respiratory Rate

Temperature, and respiratory rate, will be assessed.

8.3.4.3. Oxygen Saturation Level

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

8.3.5. 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 HR and measures PR interval, QT interval, QTcF, and QRS complex. If an ECG cannot be obtained on Day 10, it must be collected at Day 14. An ECG should be obtained for a participant having an ET visit before Day 14. 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. Post-dose ECGs should be performed within 30 to 90 minutes post-dose. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 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 8) and should be evaluated further, as clinically warranted.

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

A cardiologist may be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8.

8.3.6. Clinical Safety Laboratory Assessments

Day 1 safety laboratory assessments must be collected prior to first dose of study intervention.

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 DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events[14], version 2.1. The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

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

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

8.3.6.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Not applicable.

8.3.7. Pregnancy Testing

A serum or urine pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the

participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3.7.1. At-Home Pregnancy Testing

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. If the pregnancy test is positive, the EDP should be reported (Section 8.4.5.1). Confirm that the participant is adhering to the contraception method(s) required in the protocol.

8.3.7.2. Evaluation for Menopause

FSH is to be performed locally in female participants <60 years of age at screening who are not using hormonal contraception or hormonal replacement therapy, to confirm postmenopausal status. Female participants age 50 to 60 years with no menses for 12 months do not need FSH testing to be performed to confirm postmenopausal status.

A participant may be screened in the study prior to the test result being available as long as the FSH test result confirms postmenopausal status prior to dosing.

8.3.8. Adjunctive Therapeutic Procedures

Adjunctive therapeutic procedures will be recorded as specified in the SoA. Therapeutic procedures such as imaging, supplemental oxygen support (eg, CPAP) and transfusions should be recorded.

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

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

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

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

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

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

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

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

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

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

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety 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 should be reported as an SAE;

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

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

the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

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

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

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

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

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL of plasma, will be collected for measurement of plasma concentrations of PF-07817883 as specified in the SoA. Prior to centrifugation a 0.1 mL portion of the 4 mL of blood collected will be aliquoted for the purpose of determining the blood to plasma PF-07817883 concentration ratio at each time point as specified in the SoA. In addition, approximately 0.1 mL of blood will be collected using a micro-sampling device (TASSO M20) for the measurement of plasma concentrations of PF-07817883 at each time point as specified in the SoA. 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.

Samples will be used to evaluate the PK of PF-07817883. Each plasma sample will be divided into 2 aliquot(s) (1 each for PK, other analyses, etc). Samples collected for analyses of PF-07817883 plasma 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 other internal exploratory purposes.

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

Samples collected for measurement of plasma or whole blood concentrations of PF-07817883 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.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A 4 mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow, and if the participant signs the optional consent form.

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

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

8.7. Biomarkers

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

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

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

8.7.1. Rapid Antigen Assessments

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

Confirmed SARS-CoV-2 infection as determined by RAT using a test kit that is authorized by the sponsor in a nasal specimen collected within 2 days prior to randomization is required.

8.7.2. Specified Gene Expression (RNA) Research

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

8.7.3. Specified Protein Research

Blood will be collected for plasma biomarkers as specified in the SoA and may be used for proteomics and molecular and immunologic studies. Residuals of all samples may be banked for future research. Storage and shipping instructions will be in accordance with the laboratory manual.

8.7.4. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.5. Viral RNA Level Assessments

A NP sample will be collected per the SoA, and may be analyzed to measure SARS-CoV-2 RNA by RT-PCR. At baseline, a NP sample 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. NP samples will be collected by an HCP during an in-person visit.

If a participant is symptomatic due to COVID-19 infection at the Day 21 visit then a Day 33 NP sample should be collected.

If COVID-19 symptom worsening or recurrence occurs after completion of the 5-day treatment with study drug (ie, through Day 33), participants may subsequently attend a site for an unscheduled follow-up visit and should have NP sample collected to measure SARS-CoV-2 RNA levels.

Residual viral RNA level samples may be utilized for viral sequencing to assess the signs of viral evolution and evaluation of potential genetic viral variants including but not limited to 3CL gene, SARS-CoV-2 infectivity assays, molecular and phenotypical analysis, including host molecular or genetic analysis.

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

8.7.6. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study if the participant signs the optional consent form:

- 5 mL whole blood optimized for serum Prep B2.5.
- 2.5 ml whole blood optimized for RNA Prep R1.

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

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

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

8.8. Immunogenicity Assessments

Immunogenicity assessments are not applicable to this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypothesis

The primary hypothesis is to test whether or not there is a difference in mean change of SARS-CoV-2 RNA level from baseline to Day 5 between the PF-07817883 dose groups and the placebo group using the Bayesian dose-response model (or otherwise as specified in Section 9.3.2.2):

Null hypothesis: H_0 $\mu_{PF-07817883} - \mu_{placebo} = 0$

Alternative hypothesis: H_a $\mu_{PF-07817883} - \mu_{placebo} < 0$

Where $\mu_{PF-07817883}$ and $\mu_{placebo}$ are mean change of SARS-CoV-2 RNA level from baseline to Day 5 for each PF-07817883 dose groups and placebo group.

9.1.1. Estimands

9.1.1.1. Primary Estimand

E1 (primary analysis estimand): The estimand is the difference between the PF-07817883 dose groups and placebo in mean change from baseline in SARS-CoV-2 RNA level in NP samples in the population of non-hospitalized, symptomatic, adult participants with COVID-19 who have SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL at baseline. This analysis will exclude data after use of prohibited COVID-19 medications and study treatment discontinuation.

E2 (estimand for supplementary analyses): The estimand is the difference between the PF-07817883 dose groups and placebo in mean change from baseline in SARS-CoV-2 RNA level in NP samples in the population of non-hospitalized, symptomatic, adult participants with COVID-19. This will exclude data after use of prohibited COVID-19 medications and study treatment discontinuation.

The E2 estimand will be applied to change from baseline in SARS-CoV-2 RNA level on Days 3, 5, 10 and 14 for the supplementary analysis.

Note that for E1 and E2, partial participant data accumulated prior to use of prohibited COVID-19 medications or treatment discontinuation is included in the analysis.

9.1.1.2. Secondary Estimands

The E1 estimand will be applied to change from baseline in SARS-CoV-2 RNA level on Days 3, 10 and 14.

9.1.2. Multiplicity Adjustment

Not applicable.

9.2. Analysis Sets

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

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

Participant Analysis Set	Description
FAS	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 to which they were randomized.
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 product they actually received.
PK analysis set	All enrolled participants who received at least 1 dose of PF-07817883 and in whom at least 1 concentration value is reported.

Defined Analysis Set	Description
MFAS	All participants in the FAS who have SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL at baseline. Participants will be analyzed according to the study intervention to which they were randomized.

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. Further analysis details will be included in SAP. 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 will be reported. The number of participants randomized to the double-blind treatment phase, completing the study drug administration, completing the study, and discontinued the study will be summarized from the FAS for each 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 model will be used to analyze change from baseline outcomes. Estimated mean differences between treatments and their respective 80% CI and p-values will be calculated.

Binary endpoints will be summarized with the number and percent of participants satisfying the endpoint.

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

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

Time to event endpoints will be summarized graphically using Kaplan-Meier plots for each treatment group.

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

9.3.2.1. Definition of Endpoint(s)

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

9.3.2.2. Main Analytical Approach

The primary analysis will utilize a Bayesian Emax model applied to the estimates from the MMRM analysis.

Change from baseline in SARS-CoV-2 RNA level at Day 5 will first be analyzed using Estimand 1 and MMRM model (as per Section 9.3.1). The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Day 5 using MFAS with fixed effects including treatment, time, interaction of time by treatment, and baseline SARS-CoV-2 RNA level. Further specification of the MMRM model will be provided in the SAP. LSmeans (and 80% CIs and p-values) will be summarized.

A Bayesian Emax model will then be fitted to the Day 5 LSmeans and SEs from the MMRM analysis. Non-informative prior distributions for the placebo (E_0), the difference in response (*difTarget*) between the highest dose (600 mg q12h) and placebo, and the residual standard deviation (*sigma*).

The fitted curve will be graphically displayed with 80% credible bands. The posterior medians and 80% credible intervals (10^{th} and 90^{th} percentiles of the relevant posterior distribution) will be reported for each randomized dose (including placebo) and their differences relative to placebo. If the Bayesian Emax model cannot be fitted to the data, or the data do not support a dose-response, the model may be simplified, or the analysis may not be performed and the primary results for the study will be based on the MMRM results at Day 5. More details on how this will be assessed will be described in the SAP. No adjustments will be made for multiplicity in the MMRM model.

9.3.2.3. Supplementary Analyses

The MMRM analysis and Bayesian Emax dose-response model described in Section 9.3.2.2 will be repeated using the FAS instead of MFAS and use the E2 estimand strategy.

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

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

- Change from baseline in SARS-CoV-2 RNA level on Days 3, 10 and 14.
- Incidence of TEAEs.
- Incidence of SAEs and AEs leading to discontinuations.
- Incidence of clinically significant abnormal laboratory values, vital signs, and ECGs.

No formal statistical analysis will be conducted on any of the safety data listed above.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

Exploratory endpoints may not be reported in the CSR and may be reported separately.

Details on the definitions and analyses of the exploratory endpoints, if reported in the CSR, will be described in the SAP or equivalent analysis plan.

9.3.5. Other Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

9.3.5.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

The number (%) of participants with maximum post-dose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTcF Assessment

Degree of Prolongation	Mild (ms)	Moderate (ms)	Severe (ms)
Abs value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

9.3.6. Other Analyses

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

9.4. Interim Analyses

A planned formal interim analysis for virological response and safety may be performed to assess SARS-CoV-2 RNA level after approximately 50% or more participants, ie, at least 114 participants with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL, complete their study participation (including viral load assessment) through Day 5. The timing of the interim analysis is contingent on the recruitment rate.

Additional interim analysis may be performed for internal business decision-making or regulatory requests. Before any interim analyses are conducted, the final number and timings of interims, the details of the objectives, decision criteria, information dissemination plan, and method for maintaining the study blind as per Pfizer's SOPs will be documented and approved in an IRC charter and interim analysis plan. The study team will remain blinded to all interim results.

Participants may be discontinued from the study intervention/study as a result of the interim analysis, as described in Section 7.

9.5. Sample Size Determination

A sufficient number of participants will be screened to achieve a total of approximately 228 participants, with participants randomly assigned to PF-07817883 100, 300, or 600 mg q12h and placebo in approximately a 1:1:2:2 ratio. Assuming 20% of participants will discontinue study drug treatment or have a baseline SARS-CoV-2 RNA level <4 $\log_{10}$ copies/mL, approximately 180 participants (60 in each of PF-07817883 600 mg q12h and placebo, and 30 in each of PF-07817883 100 mg q12h and 300 mg q12h) with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL are expected to complete Day 5 of the study. Additional participants may be randomized to ensure 180 participants with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL who complete study drug treatment.

The sample size is based on the primary efficacy endpoint, change from baseline in SARS-CoV-2 RNA level at Day 5. CCI [redacted]

- CCI [redacted] ;[15]
- CCI [redacted] .[15]

Based on the above, 180 participants with baseline SARS-CoV-2 RNA level ≥4 $\log_{10}$ copies/mL who complete study drug treatment and 228 enrolled participants, in a 1:1:2:2 randomization ratio, gives acceptable operating characteristics for the study.

9.6. Analysis of Pharmacokinetic Endpoints

The PK Concentration Population is defined as all enrolled participants who received at least 1 dose of PF-07817883 and in whom at least 1 concentration value is reported. PK concentrations will be summarized and presented with descriptive statistics. A population PK modeling may be performed with the concentration data from this study alone or combined with data from other studies. In addition, a relationship between exposures and efficacy/safety endpoints may be evaluated using population PK/PD approach. Any population analyses conducted will not be part of the CSR and may be reported separately.

9.6.1. Early PK/PD Unblinding Plan

If needed, a PK/PD unblinding plan will be in place prior to the start of the PK/PD unblinding in accordance with applicable Pfizer SOPs for releasing randomization codes and breaking the study blind.

Under this plan, a group of statisticians, data programmer, PK/PD data provider, PK/PD analyst and PK/PD support would be unblinded in order to initiate the building of statistical models of the PK, dose/response as well as exposure/response analysis models and conduct associated simulations. The aim of this work would be to facilitate a fuller interpretation of the study upon completion (at appropriate interim milestone). This group will not serve on the study team during the period of early unblinding. The unblinding may occur at an appropriate time as defined in the data blinding plan to allow sufficient time for PK/PD analyses. PK/PD modeling and simulation may be used at or after the first planned interim analysis to inform dose selection for subsequent studies. If performed, these activities will only impact decisions at the program level and not impact the conduct of the ongoing study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an IRC. The IRC is independent of the study team and includes only internal members. The IRC charter describes the role of the IRC in more detail.

The IRC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the IRC 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 and investigators, as appropriate.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.8. Source Documents

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

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

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

Description of the use of the computerized system is documented in the data management plan, which is maintained by the sponsor.

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

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

10.1.9. Study and Site Start and Closure

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

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

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

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

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

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

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

10.1.10. Publication Policy

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

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary

completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

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

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

10.1.11. Sponsor's Medically Qualified Individual

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 4. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other[a]	Additional Tests (Needed for Suspected Hy's Law or DIKI)
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN or Urea Creatinine[b] Cystatin C eGFR (combined Scr+Scys) Glucose Calcium Sodium Potassium Chloride Total CO^2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein	<u>Local dipstick:</u> pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase <u>Laboratory:</u> Albumin (urine) Creatinine (urine) Urine albumin to creatinine ratio (UACR) Microscopy and culture[c]	Ferritin D-dimer hs-CRP Procalcitonin LDH CK Haptoglobin SARS-CoV-2 serology (IgM, IgG)[d] <u>At screening:</u> FSH[e] Pregnancy test (βhCG)[f]	Hy's Law AST, ALT Total bilirubin Albumin Alkaline phosphatase Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels DIKI Cystatin C eGFR Albumin (urine) Creatinine (urine) Urine albumin to creatinine ratio (UACR)

a. For Day 10 sample, only SARS-CoV-2 serology is evaluated.
b. eGFR will be calculated using the method developed by the CKD-EPI using serum creatinine.[12]
c. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
d. SARS-CoV-2 serology is evaluated with only Day 1 and Day 10 samples.
e. FSH testing is performed locally for confirmation of postmenopausal status only.
f. 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 an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.3.2. Definition of an SAE

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs 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 EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

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

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories, which are based on the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events[14], version 2.1 (July 2017):

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

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

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

SAE Reporting to Pfizer Safety via the CT SAE Report Form

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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 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, and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a WOCBP 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

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

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

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

  OR

- Is a WOCBP who agrees to use a highly effective contraceptive method (failure rate of <1% per year) with low user dependency during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

OR

- Is a WOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception 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). In addition to her use of the highly effective method above, she agrees to concurrently use an effective barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for reviewing the woman's medical history, menstrual history, and recent sexual activity in order to decrease the risk of enrolling a woman with an early, undetected pregnancy.

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

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

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

<u>Highly Effective Methods That Are User Dependent</u>

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

    - Oral + barrier*

    - Intravaginal + barrier*

- Transdermal + barrier*

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

   - Oral + barrier*

   - Injectable + barrier*

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.

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

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

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 multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

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

- The samples will be retained as indicated:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

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

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

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

10.7.2. Age-Specific Kidney Function Calculation Recommendations

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

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

Inker LA et al. N Engl J Med. 2021;385:1737-49.[16]

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms 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 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex >120 ms).
• New-onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants 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 participants 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 (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below should not be taken with PF-07817883 for the period of time at least equal to the required washout period listed in the table, and throughout the conduct of the study.

A non-exhaustive 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 judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the 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.

P-gp Substrates	Moderate to Strong CYP3A Inhibitor	Moderate to Strong CYP3A inducer
digoxin	amprenavir	apalutamide
dabigatran	amiodarone	asunaprevir and beclabuvir and daclatasvir
	aprepitant	avasimibe
	atazanavir	bosentan
	atazanavir and ritonavir	carbamazepine
	berotralstat	cenobamate
	boceprevir	dabrafenib
	casopitant	efavirenz
	ceritinib	elagolix
	cimetidine	enzalutamide
	ciprofloxacin	etravirine
	clarithromycin	ivosidenib
	cobicistat	lersivirine
	conivaptan	lesinurad
	crizotinib	lopinavir
	danoprevir and ritonavir	lorlatinib
	darunavir	lumacaftor
	darunavir and ritonavir	metamizole (dipyrone)
	diltiazem	mitapivat
	dronedarone	mitotane
	duvelisib	modafinil
	elvitegravir and ritonavir	nafcillin
	erythromycin	pexidartinib
	faldaprevir	
	fedratinib	phenobarbital

P-gp Substrates	Moderate to Strong CYP3A Inhibitor	Moderate to Strong CYP3A inducer
	fluconazole	phenytoin
	grapefruit juice	rifabutin
	grapefruit juice - *double strength*	rifampin
	idelalisib	rifapentine
	imatinib	semagacestat
	indinavir	sotorasib
	indinavir and ritonavir	St. John's wort (Hypericum perforatum)
	ipatasertib	talviraline
	isavuconazole	telotristat ethyl
	istradefylline	thioridazine
	itraconazole	tipranavir and ritonavir
	josamycin	
	ketoconazole	
	lefamulin	
	letermovir	
	lonafarnib	
	lopinavir and ritonavir	
	mibefradil	
	mifepristone	
	nefazodone	
	nelfinavir	
	netupitant	
	nilotinib	
	ombitasvir and paritaprevir and ritonavir and dasabuvir	
	posaconazole	
	ravuconazole	
	ribociclib	
	ritonavir	
	saquinavir	
	saquinavir and ritonavir	
	Schisandra sphenanthera	
	telaprevir	
	telithromycin	
	tipranavir and ritonavir	
	tofisopam	
	treosulfan	
	troleandomycin	
	tucatinib	
	verapamil	
	voriconazole	
	voxelotor	

Investigators should consult the IB for PF-07817883 for information regarding medication that is prohibited for concomitant use.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

10.10. Appendix 10: Signs and Symptoms Attributable to COVID-19

Table 5. Signs and Symptoms Attributable to COVID-19

Daily Sign and Symptom Collection[13]	Entry Criterion #4 Targeted (used for study entry)	Daily Signs and Symptom Collection
Stuffy or runny nose	X	X
Sore throat	X	X
Cough	X	X
Feeling hot or feverish	X	X
Fatigue (low energy or tiredness)	X	X
Shortness of breath or difficulty breathing	X	X
Shortness of breath (difficulty breathing) while resting		X
Shortness of breath (difficulty breathing) while physically active		X
Chest pain		X
Low energy or tiredness after physical activity		X
Difficulty concentrating		X
Chills or shivering	X	X
Muscle or body aches	X	X
Diarrhea (loose or watery stools)	X	X
Nausea (feeling like you wanted to throw up)	X	X
Vomiting (throw up)	X	X
Headache	X	X
Loss of smell		X
Loss of taste		X

Sustained alleviation of all targeted signs and 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. Missing severity at baseline will be treated as mild.

The decision to require 4 consecutive days with all targeted symptoms absent or alleviated 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. The outcome measure requires 4 consecutive days of targeted symptoms being reported as alleviated or resolved. This definition may be updated based on regulatory feedback/interactions and will be described in the SAP.

Sustained resolution of all targeted signs and symptoms is defined as the event occurring on the first of 4 consecutive days when any symptoms scored as absent, mild, moderate or severe at study entry are scored as absent.

Progression to a worsening status for any targeted symptom will be derived programmatically based upon increasing severity (ie, the first time any targeted symptom worsens after treatment relative to baseline):

Progression to worsening (Yes/No)	
Increasing severity	Yes
Not increasing severity	No

Symptom recurrence will be assessed using 2 different definitions:

1. Sponsor definition: Any improvement in targeted COVID-19 signs and symptoms that subsequently worsened (total symptom score increased by ≥4).

2. FDA definition: After achieving short symptom recovery (the first day of at least two consecutive diary entries where all targeted symptoms are absent), symptom rebound is the first day of at least two consecutive diary entries after Day 5 where there is any targeted symptom (regardless of severity), or when a subject is hospitalized after symptom recovery.

10.11. Appendix 11: Definition of Viral RNA Rebound

Viral RNA rebound will be assessed using the following FDA-based definition, based upon the FDA analysis of the ADMC and ADSL datasets from NDA 217188. This approach accounts for the impact of antiviral therapy on early viral RNA decline.

Within the population of Day 5 virologic responders (Day 5 VL <LLOQ or $\geq$1 $\log_{10}$ copies/mL decline from baseline to Day 5), virologic rebound is defined as:

1) Day 5 VL <LLOQ AND at Day 10, 14, or 21 VL $\geq$LLOQ;

OR

2) Day 5 RNA $\geq$LLOQ AND Day 10, 14, or 21 RNA $\geq$0.5 $\log_{10}$ copies/mL increase from Day 5.

10.12. Appendix 12: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 1 (24 March 2023)

Overall Rationale for the Amendment: To update prohibited concomitant medications in line with emerging PK data and incorporate regulatory feedback.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Addition of PK data from PART-5: DDI (midazolam) of Study C5091001.	To update the Clinical Overview with emerging PK data.	Section 2.2.2. Clinical Overview
Deletion of text prohibiting use of medications highly dependent on CYP3A4 for clearance with narrow TI during study.	PF-07817883 does not have CYP3A4 perpetrator risk based on midazolam DDI.	Section 6.9 Prior and Concomitant Therapy
Deletion of text prohibiting use of hormonal contraceptives during study.	PF-07817883 does not have CYP3A4 perpetrator risk for enzyme induction.	Section 6.9 Prior and Concomitant Therapy
Addition of text to allow use of hormonal contraceptives during study.	PF-07817883 does not have CYP3A4 perpetrator risk.	Appendix 4
Addition of inclusion criterion #5, addition of new exclusion criterion #2, revision of exclusion criterion #11 and clarification of therapy permitted and prohibited during the study.	To address comments received from the FDA.	Section 1.1 Synopsis, Section 5.1 Inclusion Criteria, Section 5.2 Exclusion Criteria, Section 6.9 Prior and Concomitant Therapy and Section 7.1 Discontinuation of Study Intervention
Addition of assessments for viral RNA rebound and symptom recurrence as exploratory objectives and endpoints in Section 3. Corresponding addition of definitions for symptom recurrence to Appendix 10	To address comments received from the FDA.	Section 3 Objectives, Endpoints, and Estimands, Section 10.10 Appendix 10 Signs and Symptoms Attributable to COVID-19 and Section 10.11 Appendix 11 Definitions of Viral RNA Rebound.

Description of Change	Brief Rationale	Section # and Name
and addition of definitions for viral RNA rebound to new Appendix 11.		
Addition of SARS-CoV-2 RNA level assessments at Day 21 and Day 33, with corresponding edit of Day 21 visit from "T" to "S/P" and Day 33 visit from "T" to "S/P/T".	To address comments received from the FDA.	Section 1.3 SoA SARS-CoV-2 RNA level assessment (NP) and Study Visit Location
Addition of targeted physical exam and vital signs assessment at Day 21 site visit and Day 33 visit if participant is still symptomatic.	To address comments received from the FDA.	Section 1.3 SoA Targeted physical examination and Vital signs
Addition of instructions to sites for collecting unscheduled NP samples in the case of symptom worsening or recurrence.	To address comments received from the FDA.	Section 8.7.5 Viral RNA Level Assessments
Addition of a PK sample by TASSO micro-sampling before administration of second dose of PF-07817883.	To address comments received from the FDA.	Section 1.3 SoA PK micro-sampling
Addition of optional Day 21 assessment.	To address comments received from the FDA.	Section 1.3 SoA Retained research samples for biomarkers (Prep B2.5, prep R1)
Addition of AE assessments at Days 2 and 4.	AEs will be assessed if optional Day 2 and 4 visits occur.	Section 1.3 SoA Serious and nonserious AE monitoring
Removed need for participant to check temperature.	Fever will be captured as part of the daily signs and symptoms collection through the "feeling hot or feverish" symptom. To avoid duplication of data, the participant will not measure their temperature.	Section 8.2.3 Daily Signs and Symptoms of COVID-19 and Section 8.3.4.4 At-Home Devices for Vital Signs.

Description of Change	Brief Rationale	Section # and Name
Removed recording of documented fever in Daily Signs and Symptom Collection and as part of Entry Criterion. Removed correlating footnote.	Fever will be captured as part of the daily signs and symptoms collection through the "feeling hot or feverish" symptom. To avoid duplication of data, the participant will not measure their temperature.	Section 10.10 Appendix 10 Signs and Symptoms Attributable to COVID-19
Removed need for participants to be supplied with a pulse oximeter.	Oxygen saturation will be checked during all in-person site visits.	Section 8.3.4. Vital Signs and Section 8.3.4.4 At-Home Devices for Vital Signs
Addition of eGFR (combined Scr+Scys) and albumin assessments and edits to collect cystatin C post-baseline at each lab assessment.	Updates to kidney function assessments as per guidance from Pfizer Kidney Safety Council recommendation.	Section 10.2 Appendix 2 Clinical Laboratory Tests
Nonsubstantial Modification(s)		
Added text from Exclusion Criterion #15 into Section 1.3 SoA Notes for Safety Laboratory Assessments row.	Clarification of this text is to provide guidance surrounding laboratory assessments.	Section 1.3 SoA Safety Laboratory Assessments
Edited "Study Visit Location" for Day 2 and 4 optional visits from "NA" to "T".	Clarification that these optional visits may be conducted by telehealth.	Section 1.3 SoA Study Visit Location
Addition of "Day 1" to the SoA Notes column.	Clarification that post-dose ECGs should be performed within 30 to 90 mins post-dose on Day 1.	Section 1.3 SoA 12-lead ECG
Edited "NP" to "nasal".	Clarification that a nasal sample is required for the selected RAT kit used at screening.	Section 1.1 Synopsis, Section 1.3 SoA, Section 5.1 Inclusion Criteria and Section 8.7.1 Rapid Antigen Assessments
Deletion of "predicted" and "preliminary" for toxicity margin text and edit "total" to "unbound" for C_{max} and AUC_{24} values.	Clarification edits to align with Investigators Brochure Version 2 updates.	Section 2.2.1 Nonclinical Studies of PF-07817883

Description of Change	Brief Rationale	Section # and Name
Addition of description on use of PK/PD modeling and simulation results.	Clarification that PK/PD modeling and simulation results would only impact dose selection decisions at a program level and not the protocol level [ie, current study]).	Section 9.6.1 Early PK/PD Unblinding Plan
Addition of sponsor's address.	To comply with new regulatory requirements.	Title page
Edits throughout Section 10.1 Appendix 1.	To comply with new regulatory requirements.	Section 10.1 Appendix 1 Regulatory, Ethical and Study Oversight Considerations
Minor edits to clarify protocol text and correct minor errors and typos from previous versions.	To clarify protocol text and correct inadvertent errors.	Several sections throughout

10.13. Appendix 13: Abbreviations

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

Abbreviation	Term
%CV	percent coefficient of variation
µM	micromolar
3CL	3C-like
Abs	absolute
AE	adverse event
CCI	[redacted]
AKI	acute kidney injury
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC_{24}	area under the concentration-time curve from time zero to 24 hours (1 day)
CCI	[redacted]
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CCI	[redacted]
CAR	chimeric antigen receptor
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL_r	renal clearance
C_{max}	maximum observed concentration
CO^2	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

Abbreviation	Term
CT	clinical trial
CTIS	Clinical Trial Information System
C_{trough}	drug concentration observed at the last planned timepoint prior to dosing
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DAIDS	Division of AIDS
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
difTarget	difference in response between the highest dose (600 mg q12h) and placebo
dNHBE	differentiated normal human bronchial epithelial cells
DU	dispensable unit
E1	primary analysis estimand
E2	estimand for supplementary analyses
EC	ethics committee
EC_{50}	drug concentration at which 50% inhibition of viral replication is observed; concentration required for 50% effect
EC_{90}	drug concentration at which 90% inhibition of viral replication is observed; concentration required for 90% effect
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
eDiary	electronic diary
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ePRO	electronic patient reported outcomes
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EUA	Emergency Use Authorization
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FAS	full analysis set
FDA	Food and Drug Administration

Abbreviation	Term
FE	food effect
FIH	first-in-human
FSH	follicle-stimulating hormone
fu	fraction unbound
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
CCI	[redacted]
HCoV	human coronavirus
HCP	healthcare provider
HCT	hematopoietic cell transplantation
HIV	human immunodeficiency virus
hr	hour
HR	heart rate
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ID	identification
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRC	internal review committee
IRT	Interactive Response Technology
IV	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KO	knock out
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LFT	liver function test
LLOQ	lower limit of quantitation
LS	least-squares
mAb	monoclonal antibody
MAD	multiple ascending dose

Abbreviation	Term
ME	metabolism and excretion
MERS	Middle East Respiratory Syndrome
MFAS	modified full analysis set
mg	milligram
mIU/mL	milli-international units per milliliter
mL	milliliter
mm^3	millimeter cubed
MMRM	mixed model for repeated measures
MOA	mechanism of action
M^{pro}	main protease
MQI	medically qualified individual
ms	milliseconds
MTD	maximum tolerated dose
NA	not applicable
NDA	New Drug Application
CCI [redacted]	
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
NP	nasopharyngeal
NR	not reportable
CCI [redacted]	
PD	pharmacodynamic(s)
P-gp	p-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PR	pulse rate
PRO	patient reported outcomes
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
q12h	every 12 hours
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
qual	qualitative
RAT	rapid antigen testing
rBA	relative bioavailability
RBC	red blood cell
RNA	ribonucleic acid
RT-PCR	reverse transcriptase–polymerase chain reaction
[S]	investigational site
SAD	single ascending dose
SAE	serious adverse event

Abbreviation	Term
SAP	Statistical Analysis Plan
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
Screat	serum creatinine
Scys	serum cystatin C
SD	single dose
SE	standard error, supratherapeutic exposure
SoA	schedule of activities
SoC	standard of care
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
[T]	telehealth visit
T bili	total bilirubin
TEAE	treatment-emergent adverse event
CCI [redacted]	
TMPRSS2	transmembrane serine protease 2
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
CCI [redacted]	
VeroE6	monkey kidney cells E6
VL	viral load
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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