A PHASE 1B, 2-PART, DOUBLE-BLIND, PLACEBO-CONTROLLED, SPONSOR-OPEN STUDY, TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SINGLE ASCENDING (24-HOUR, PART 1) AND MULTIPLE ASCENDING (120-HOUR, PART 2) INTRAVENOUS INFUSIONS OF PF-07304814 IN HOSPITALIZED PARTICIPANTS WITH COVID-19

Study Intervention Number:	PF-07304814
Study Intervention Name:	N/A
US IND Number:	CCI [redacted]
EudraCT Number:	2020-003905-73
Protocol Number:	C4611001
Phase:	Phase 1b

Short Title: A Phase 1b First-In-Human Study to Evaluate Safety, Tolerability, And Pharmacokinetics Following Single Ascending And Multiple Ascending Doses, of PF-07304814 In Hospitalized Participants With COVID-19

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 4	15 December 2020	This amendment is undertaken following acquisition of 14-day toxicology data and discussions with regulatory authorities which allowed for the study design to include the possibility of escalating the dose in Part 2. All sections of the protocol were impacted. The substantial changes are presented below: 1. Updated study design to replace Part 2 designation from "Extended Infusion" to "Multiple Ascending Dose (MAD)" (all sections). 2. Updated study design to add 1 additional planned cohort and 1 additional optional cohort in Part 2 making a total of 2 planned and 2 optional cohorts in Part 2. (Section 1 and Section 4). 3. Updated planned number of participants from 56 to 72 to account for 2 additional cohorts being added in Part 2 (Section 1 and Section 4). 4. Added starting dose in first cohort in Part 2, Cohort 6 (Section 1 and Section 4). 5. Updated non-clinical and clinical overview summaries (Section 2). 6. Updated benefit/risk assessment (Section 2). 7. Added statement that any dose escalation decision in Part 2 will occur only after discussion with competent regulatory authorities, thereby removing the need for IRC in Part 2. 8. Updated dose escalation and stopping rules to address both Part 1 and Part 2 (Section 6). Other substantial changes: 1. Added additional study intervention formulation (powder form) to be used for participants enrolled in

		Part 2 only (Section 6). 2. Added 2 additional timepoints in Part 2 SoA, and therefore, total blood draw volume for biomarker sampling (Section 1.3 and Section 8) to align with safety assessments. This will provide additional data for markers involved in disease process eg, inflammation or bacterial infection etc. 3. Added 1 additional time point for ECG assessment in Part 2 SoA, to align with safety assessment collections (Section 1.3). This will reduce the burden on the participant and the site by having all assessments in same interaction. Non-substantial changes: CCI [redacted] 2. Added clarification of timing of PK draws in Part 2 SoA Table. 3. Added additional row in Part 2 SoA Table as "Serum PD Biomarker – Serology" as the timepoints for collection were different than other Serum PD Biomarker assessments. 4. Updated overall study design figure to reflect the dose being evaluated in Cohort 3 (Section 1.2) in order to align with the Protocol Administrative clarification Letter (dated 08-Nov-2020). Few typographical errors were noted and fixed.
Amendment 3	05 November 2020	This amendment is making the following substantial changes: • **Sections Impacted:** **Section 1.3: SoA Table Part 1: SAD and Part 2: Extended Infusion** **Section 8: Study Assessments and Procedures** **Changes:** i. Removed optional PK blood draw at 2 hr and

		required PK blood draw at 12 hr and 32 hr in Part 1: SAD (24-h infusion). ii. Removed PK blood draws at 12 hr and 132 hr in Part 2: Extended Infusion (120-h infusion). iii. Updated total blood sampling volume to account for reduced PK blood draws. **Rationale**: The frequency of blood draws reduced as per request by the FDA. • **Sections Impacted:** **Section 1.3: SoA Table Part 2: Extended Infusion** **Section 10.2: Clinical Laboratory Tests** **Change**: Added coagulation panel as additional assessment. **Rationale**: The assessment frequency of coagulation markers was increased to align with other safety labs in Part 2. • **Sections Impacted:** **Section 1.2: Schema** **Section 2.3: Benefit/Risk Assessment** **Section 4.1: Overall Design** **Section 4.3: Justification for Dose** **Changes:** i. Changed number of planned Cohorts in Part 1 from 3 to 2 and number of optional cohorts from 2 to 3 – in Schema. ii. Updated highest planned dose in Part 1 from 5000 mg to 1000 mg. iii. Removed the values/estimations of doses for Cohort 3 in Part 1 and Cohort 6 and 7 in Part 2. **Rationale**: Due to the revised PK stopping limits and to align with feedback received from the FDA, doses higher than 1000 mg will be determined after review of the safety and PK data of previous cohorts. For Part 1, these newly identified doses may be evaluated

		in optional cohorts (Cohort 3-5) in Part 1. Doses in Part 2 (Cohort 6 and Cohort 7) will be determined after careful review of available data from Part 1, as well as emerging data from study C4611007 and agreement with the competent regulatory authority. • **Sections Impacted:** **Section 2.2.1.3: Non-clinical Safety** **Section 2.2.2: Clinical Overview** **Section 4.3: Justification for Dose** **Section 6.6: Dose Modification** **Change**: PK stopping limits revised to align with exposures from the 70 mg/kg 14-day continuous infusion in non-human primates. **Rationale**: The purpose to lower the PK stopping limits of the study is to limit participant risk and is in alignment with feedback received from the FDA. • **Sections Impacted:** **Section 2.3: Benefit/Risk Assessment** **Section 5.2: Exclusion Criteria** **Changes:** i. Added the additional risk of thrombotic event, DVT or PE, due to study intervention. ii. Added exclusion criterion for participants with history of venous thromboembolic event, including deep venous thrombosis or pulmonary embolism. **Rationale**: Changes made to reduce overall participant risk as the study population is at higher risk of developing thrombotic complications as a result of disease progression. • **Sections Impacted:** **Section 5.2: Exclusion Criteria** **Section 6.5: Concomitant Therapy** **Section 10.4 Female Participant Reproductive Inclusion Criteria** **Change**: Added criteria to exclude women using

		hormonal therapy as contraception method or as replacement therapy to manage post-menopausal symptoms. **Rationale**: Hormones used for female contraception or as replacement therapies may increase the risk of developing thrombotic events. • **Sections Impacted:** **Section 3: Objectives, Estimands, and Endpoints** **Section 9.4.2. Secondary Endpoint: Pharmacokinetic Analyses** **Change:** Plasma PK parameters from Part 1 updated. Only C24 and C24 (dn) will be reported. **Rationale:** Due to reduced PK sampling in Part 1, some PK parameters cannot be accurately estimated, therefore, not reported. This amendment is making the following non substantial changes: • **Sections Impacted** • **Section 1.3: Schedule of Activities (Part 1 and Part 2)** • **Section 8.2.3: Electrocardiograms** **Change**: Added additional time window for ECG assessments. • **Sections Impacted:** **Section 1.2: Schema** **Section 4.1.1: Overall Design Part 1: SAD** **Change:** Changed 1.0-fold to 1-fold • **Section 2.2.2: Clinical Overview** **Change**: Changed the sentence from "The study is planned to begin in Oct-2020" to "The study began in Oct-2020" to align with the Amendment date.
Amendment	16 October	This amendment is making the following substantial

2	2020	changes: • **Sections Impacted:** **Section 1.3: SoA Table** **Section 8: Study Assessments and Procedures** **Change:** i. Removed PK blood draws at 0.5 hr, 26 hr, and 30 hr and made 2 hr PK blood draw optional in Part 1: SAD (24-h infusion). ii. Made 6 hr blood draws for selected biomarkers (including plasma PD biomarker, serum PD biomarker, and banked biospecimen [Prep D1]) optional in Part 1: SAD (24-h infusion). iii. Removed biomarker blood collection for specified viral genetics in Part 1: SAD (24-h infusion) and Part 2: Extended Infusion (120-h infusion). iv. Removed 12-lead triplicate ECG assessments at 0.5 hr and 2 hr timepoints in Part 1: SAD (24-hr infusion). **Rationale**: The frequency of blood draws reduced or made optional to lessen burden on the patient. Similarly, frequency of collection of ECG reduced on Day 1 to lower the burden on the site coordinator/nurse and to limit the contact with the patient. • **Sections Impacted**: **Protocol Title** **Section 1: Protocol Summary (Synopsis)** **Section 2: Introduction** **Section 4: Study Design** **Section 5: Study Population** **Change**: Broadened the inclusion range of patient severity by allowing patients with severe symptoms of COVID-19, with some limitations. • Removed exclusion criterion #1d. CCI [redacted]

		CCI [redacted] • **Section 2.2.2: Clinical Overview:** **Change:** Added summary of planned study, C4611007. **Rationale**: The newly planned study in healthy volunteers will use PF-07304814 for 24-h infusion and therefore, safety data obtained from this study will be relevant to this study, C4611001. • **Section 2.3: Benefit/Risk Assessment:** **Change**: Added risk for the use of central venous catheter or midline, if used for blood draws. **Rationale**: The patient population included in the study may be at increased risk of clotting. Hence, additional risks are added to the benefit/risk profile. • **Section 2.3: Benefit/Risk Assessment:** **Change**: Added risk of exacerbation of a pro-inflammatory state on extended infusion at higher doses. CCI [redacted]

		• **Sections Impacted**: **Section 1: Protocol Summary (Schema)** **Section 4: Study Design** CCI [redacted] [redacted] • **Sections Impacted**: **Section 2: Introduction** **Section 5: Study Population** **Change:** Added reference to new COVID-19 treatments which have received Emergency Use Authorization by the FDA, to-date. **Rationale**: Several new treatments are developed and have received EUA since the previous amendment. These treatments are added in the Background Section and use of these therapies are now permitted, as part of SoC or open-label use. • **Section 5.2 Exclusion criteria:** **Change:** Added additional exclusion criterion. **Rationale**: Provided further modification to not only exclude patients currently with critical respiratory disease, but to also exclude those expected to rapidly deteriorate after hospital admission and study enrolment. • **Sections Impacted**: **Section 6: Study Intervention** **Section 8: Study Assessments and Procedures** **Change**: Added clarifications that (i) central or midline catheterization is not needed to draw blood, if not clinically warranted and (ii) study intervention should be given through contralateral arm from PK

		draws. **Rationale**: The need for central or midline catheterization for blood draws was not clearly defined in the protocol. • **Section 6.6: Dose Modification:** **Change**: Updated safety margins for dose escalation and stopping rules. CCI [redacted] • **Sections Impacted:** **Section 1.3: Schedule of Activities Tables** **Section 8.8.5.2: Serum PD Biomarker Assessments:** **Change:** Added Haptoglobin to serum PD biomarkers. CCI [redacted] • **Section 9.4.2: Secondary Endpoint:** **Change**: Updated method of determination for Vss. **Rationale**: Updated text to correct typographical error. • **Section 9.6: Data Monitoring Committee or Other Independent Oversight Committee:** **Change**: Added reference of C4611007. **Rationale**: As C4611001 and C4611007 are being conducted concurrently, it is planned that the IRC will also consider any unexpected safety findings from the study C4611007. • **Section 11: References:** **Change**: Updated reference #10.

		Rationale: Reference #10 was updated as final report is available.
Amendment 1	21 September 2020	This amendment is making the following substantial changes: [redacted] • **Sections Impacted**: **Section 1.3**; SoA Table for PART 1: SAD (24-h infusion) and PART 2: Extended Infusion (120-h infusion) **Section 1.1**; Synopsis **Section 1.2**; Study Schema **Section 3**; Objectives, Estimands, and Endpoints Table. **Change**: Extended the screening window from *Day -2 to Day 1 to Day -3 to Day 1.* **Rationale**: The day added to the screening window will allow for flexibility in dosing to occur on a weekday, in the event that screening occurs over a weekend or a holiday and personnel resources are unavailable during that time. • **Section**: **1.3**; SoA Table for PART 1: SAD (24-h infusion). **Change:** Allowed 0.5 hr PK collection to be optional. **Rationale**: The optional collection will reduce the burden on sites. • **Section**: **5.1**; Inclusion Criterion #1. **Change**: Increased the upper age limit from 75 to

		79 years. **Rationale**: Due to increased number of cases and increased risk of SARS-CoV-2 infection with increasing age, the current limit of 75 years of age in hospitalized patients had proved limiting in enrollment. Therefore, based on feedback from site investigators, the upper age limit in the study has been increased from 75 to 79 years. Although the age limit is being increased to enhance recruitment, this will be limited to those with BMI <35 kg/m2 in the 76-79 age range to minimize the risk of including a frail population with concurrent significant co-morbidities. • **Section**: **5.1**; Inclusion Criterion #3. **Change**: Option of additional tests for confirmation of SARS-CoV-2 infection, including antigen-based test are allowed. **Rationale**: As new methods and tests are being developed and receiving approval for use, option of additional tests is added accordingly. [redacted]

		CCI [redacted] • **Section: 5.1**; Inclusion Criterion #6. **Change**: Increased the BMI upper limit from 35 kg/m^2 to 40 kg/m^2. **Rationale**: Due to increased number of cases and increased risk of SARS-CoV-2 infection in individuals with underlying co-morbid conditions, especially obesity, CV and diabetes, the current limit of 35 kg/m^2 had proved limiting in enrollment. Therefore, based on feedback from site investigators, the upper limit of BMI for the participants to be included in the study has been increased. • **Section**: **5.2**; Exclusion Criterion #1. **Change**: Added sub-bullet to with signs of severe disease. **Rationale**: Additional signs will further clarify that participants with severe form of disease are exclusionary. • **Section: 7.1**; Discontinuation of Study Intervention. **Change**: Addition of an option for stopping treatment and discontinuing the participant due to anaphylaxis or a serious allergic reaction, during treatment. **Rationale**: In this study, PF-07304814 is being infused for the first time in humans, therefore, the full range for toxicities are not known yet. Hence, among other adverse reactions, the investigators should regard anaphylaxis as a possible risk. • **Section**: **10.8**; Appendix 8: Prohibited Medications. **Change**: Included the drug-drug interaction management plan for concomitant medications metabolized primarily via CYP3A, as well as those which are substrates of P-gp, BCRP, OATP1B1/1B3, OCT1, and MATE1/2K

		transporters. **Rationale**: PF-00835231 has the potential to be a time-dependent inhibitor of CYP3A and inhibitor of P-gp, BCRP, OATP1B1/1B3, OCT1, and MATE1/2K transporters at higher doses. Therefore, additional text was included to highlight this possible risk. This Amendment is making the following non-substantial changes: • **Section**: **5.2**; Exclusion Criterion #12. **Change:** Clarification that investigational drugs/treatments used as for COVID-19 treatment are allowed, when these are given as part of an open-label study. • **Section 8.5;** Pharmacokinetics. **Change**: K_2EDTA changed to K_3EDTA to correct a typographical error. • **Section 9.6;** Data Monitoring Committee or Other Independent Oversight Committee. **Change**: deleted "internal" from independent IRC as it was a typographical error. • **Section 10.2**; Appendix 2: Clinical Laboratory tests. **Change**: Removed fasting requirement from glucose (in Table 10). **Change**: Added phosphorus to clinical chemistry tests, as requested by the FDA. • **Section 10.4.4**; Appendix 4: Contraception Methods. **Change**: Replaced bullets to a numbered list of contraception methods.
Original protocol	04 August 2020	N/A

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

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1b First-In-Human Study to Evaluate Safety, Tolerability, And Pharmacokinetics Following Single Ascending And Multiple Ascending Doses, of PF-07304814 In Hospitalized Participants With COVID-19.

Rationale: The current study is the first clinical administration with PF-07304814 (prodrug), and its active moiety, PF-00835231, is a potent and selective inhibitor of the SARS-CoV-2 3CL protease. It is designed as a 2-part study in hospitalized COVID-19 patients as a randomized, double-blind, sponsor-open, parallel group, placebo-controlled trial. Part 1 is to evaluate safety, tolerability, PK and markers of clinical activity of escalating doses of PF-07304814 given as 24-hour IV infusions. Part 2 is to evaluate safety, tolerability, PK and markers of clinical activity of escalating doses of PF-07304814 given as 120-hour IV infusions.

Objectives, Estimands, And Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To assess the safety and tolerability following single and multiple ascending doses of PF-07304814 in hospitalized participants with COVID-19.	N/A	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs (including infusion site reactions). • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements, pulse oximetry/SpO_2, and 12-lead ECG parameters.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the plasma PK of PF-07304814 and PF-00835231 and urinary PK of PF-00835231 following single and multiple ascending doses in hospitalized participants with COVID-19.	N/A	**Part 1: SAD** • PF-07304814 (prodrug) and PF-00835231 (active moiety) plasma PK: C_{24} (end of infusion) and C_{24} (dn). • PF-00835231 urinary PK parameters: Ae, Ae%. **Part 2: MAD** • PF-07304814 (prodrug) and PF-00835231 (active moiety) plasma PK: C_{120} (end of infusion), C_{max}, C_{ss}, and $t_{½}$.
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
[redacted]	[redacted]	[redacted]

Objectives	Estimands	Endpoints
CCI [redacted]		[redacted]
• Measurement of SARS-CoV-2 viral load (by RT-PCR) and, if feasible, molecular analysis in nasopharyngeal swab and saliva samples over time.	N/A	• SARS-CoV-2 viral load (RT-PCR) and, if feasible, molecular analysis in nasopharyngeal swab and saliva (at Screening, Days 1, 2, 3 and 6 for **Part 1: SAD**, and at Screening, Days 1, 3, 6, 7, 10, 14 and last follow-up for **Part 2: MAD**.
• Measurement of exploratory biomarkers.	N/A	• Change from baseline in biomarkers (on Days 1, 2, 3 and 6 for **Part 1: SAD**, and Days 1, 3, 6, 7, 10, 14 and last follow-up for **Part 2: MAD** may include: • Cytokines of inflammatory response (eg, IL-1B, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13TNF-α, and IFNγ); • Coagulation (eg, PT, aPTT, D-dimer), fibrinogen and haptoglobin; • Generalized endothelial damage/anemia (eg, ferritin); • Cardiac dysfunction (eg, CK, proBNPII, and troponin); • General markers of sepsis/organ damage (eg, LDH, hsCRP, and cystatin-C), procalcitonin; • Serological endpoints: anti-SARS CoV-2; CCI [redacted]
[redacted]	CCI	[redacted]
[redacted]	[redacted]	[redacted]

Overall Design:

This is a First-In-Human Phase 1b study to evaluate the safety, tolerability and PK of PF-07304814 in participants who are hospitalized for treatment of COVID-19. The participants will be receiving SoC therapy for the treatment of mild, moderate, or severe COVID-19, but will not be eligible if they require mechanical ventilation or ECMO at screening or baseline. All participants will have a confirmed positive test for SARS-CoV-2 (see Section 5.1 for details) and onset of symptoms within 15 days of Screening. For inclusion into **Part 2: MAD** of the study, participants will be required to have had a positive test for SARS-CoV-2 (see Section 5.1 for details) within 72 hours prior to Screening.

This is a 2-part study in which up to a total of approximately 72 participants on SoC are planned to be enrolled. It is a randomized, double-blind, sponsor-open, parallel group, placebo-controlled trial. Part 1 is to evaluate safety, tolerability, and PK of escalating doses of PF-07304814 given as 24-hour IV infusions. Two planned and 3 optional cohorts with 8 participants/cohort will be included in **Part 1: SAD** (24-h continuous infusion). Precautionary **sentinel** dosing will be used in each dose-escalating cohort in **Part 1**. A small cohort of 2 participants (1 receiving PF-07304814 and 1 receiving placebo) within a cohort will be dosed prior to the remainder of the cohort. **Part 2: MAD** is to evaluate safety, tolerability, and PK of multiple ascending doses of PF-07304814 given as 120-hour IV infusions. Two planned and 2 optional cohorts with 8 participants/cohort will be included in **Part 2**.

Number of Participants

A maximum of approximately 72 participants will be enrolled to study intervention such that approximately 72 evaluable participants complete the study.

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. 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.

Participants who discontinue during the trial for reasons other than drug-related safety events may be replaced at the discretion of the Sponsor and Investigator.

Intervention Groups and Duration

Part 1: SAD Cohorts of 8 participants each who meet the eligibility criteria will be enrolled. The 2 sentinel participants will be randomized in a PF-07304814:placebo ratio of 1:1, while the remaining 6 participants will be randomized in a ratio of 5 (PF-07304814):1 (placebo). Both treatments will be administered in a telemetered (for 12 hours post the start of dosing) setting as a continuous IV infusion for 24 hours for each dose, in addition to SoC therapy. They will be required to stay in hospital from at a minimum, Day 1, pre-dose (at least

2 hours) through completion of Day 3 evaluations (Follow-up 1). Participants will then return for Day 6 (Follow-up 2) activities and a planned final follow-up visit per the SoA on Day 30-37 (Follow-up 3) for a total of approximately 4-5 weeks study participation from first dose to follow-up, excluding screening.

Part 2: MAD Cohorts of 8 participants each who meet the eligibility criteria will be enrolled and randomized in a PF-07304814:placebo ratio of 6:2. Participants will be required to stay in hospital from, at a minimum, Day 1, pre-dose through completion of Day 7 evaluations (Follow-up 1). Participants will then return for Day 10 (Follow-up 2) and Day 14 (Follow-up 3) activities and a final planned follow-up (Follow-up 4) visit per the SoA on Days 34-41 for a total of approximately 5-6 weeks study participation from the start of dosing to follow-up, excluding screening.

Data Monitoring Committee or Other Independent Oversight Committee: IRC

This study will use an IRC, which is independent of the study team and includes Pfizer internal members. In Part 1, emerging data will be reviewed by the Investigator(s) (if available), the study team and the IRC. The independent IRC will assess whether it is safe to proceed to continued dosing within a cohort following sentinel dosing and whether it is safe to dose-escalate to the next dose level. The IRC may also be consulted at other times to review safety data.

Statistical Methods

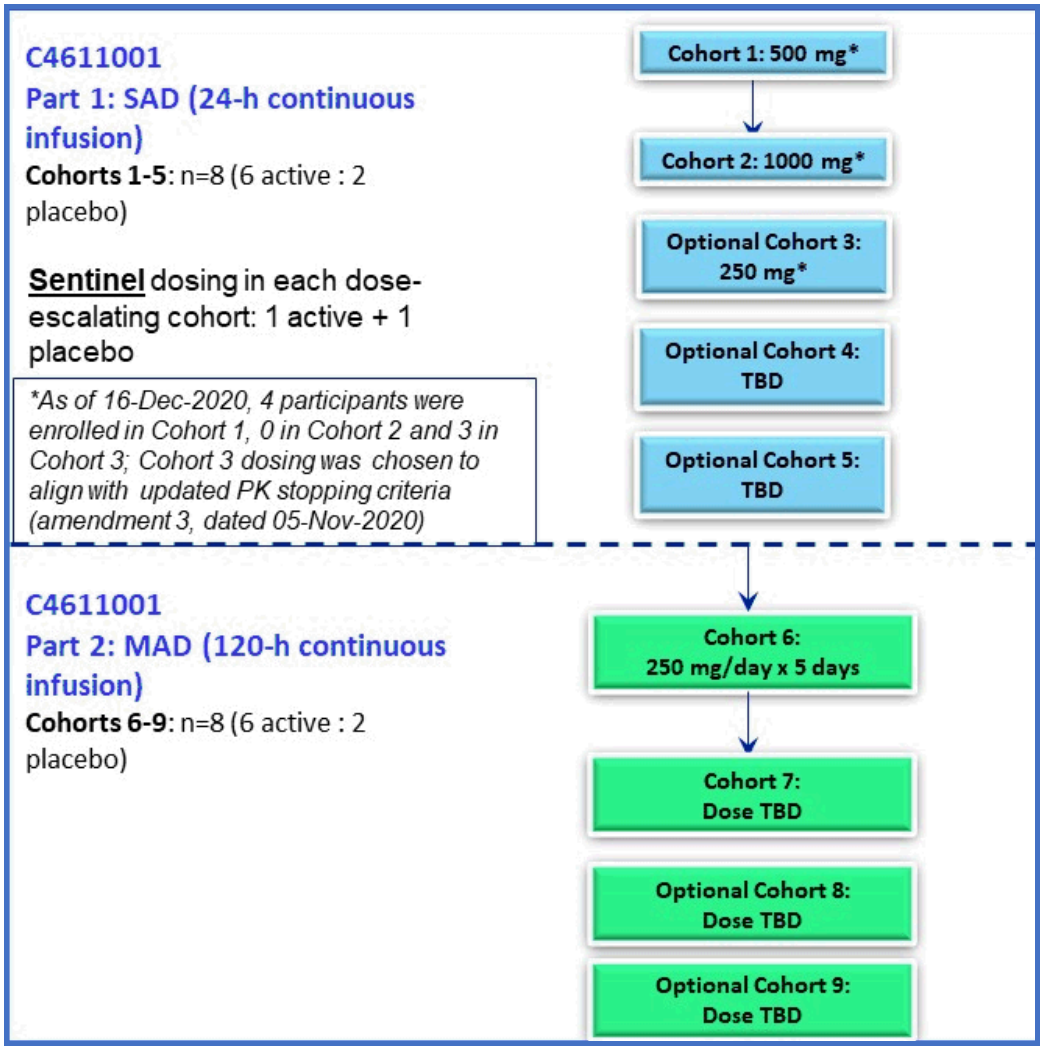
The sample size for both parts of the study has been chosen based on the need to minimize first exposure to humans of a new chemical entity and the requirements to provide adequate safety and toleration information at each dose level.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. No formal analyses are planned for safety data.

PK parameters of PF-07304814 and PF-00835231 will be derived following 24- and 120-hour infusions. The PK data for PF-07304814 and PF-00835231 will be reported separately and will be listed and descriptively summarized as required. No formal inferential statistics will be applied to the PK data.

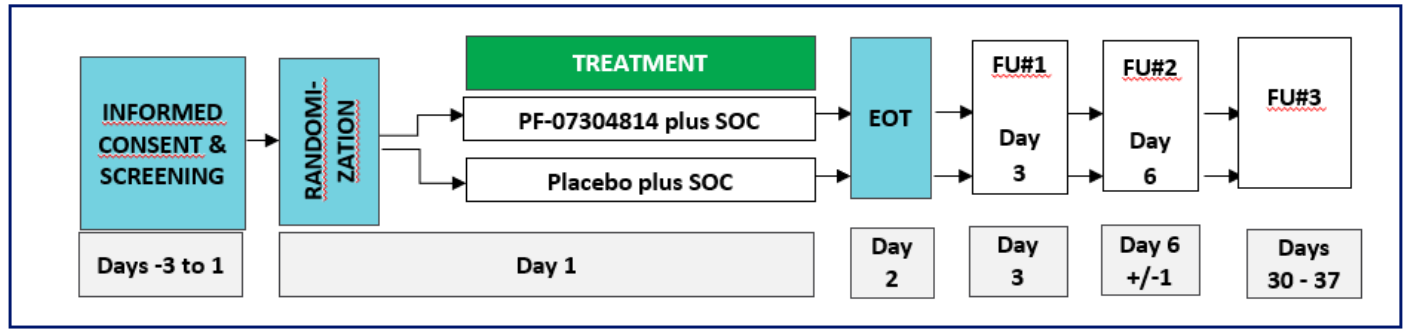
1.2. Schema

Overall Study Design of C4611001

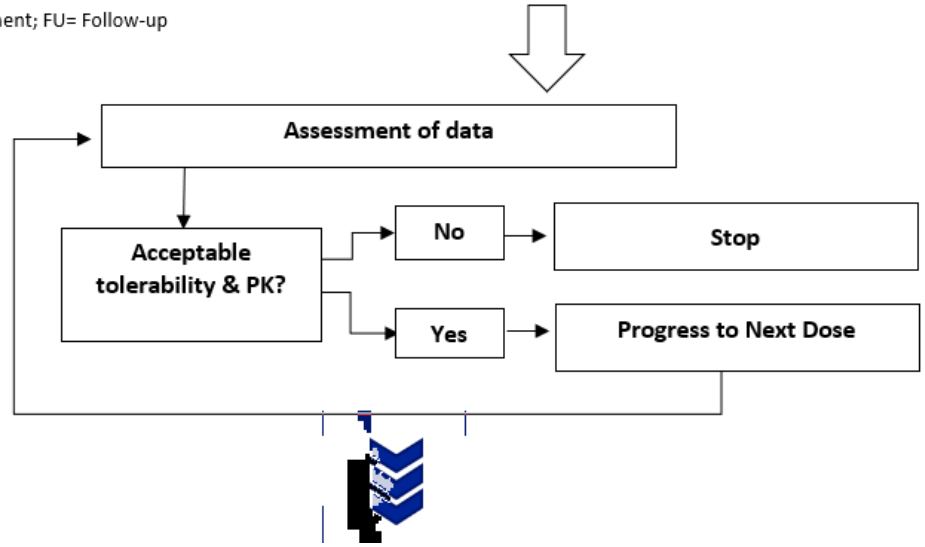


Doses and dosing scheme presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data. The projected exposures (adjusted based on observed PK) at the modified doses as well as those for the optional cohorts will not exceed the exposure limits agreed with competent regulatory authorities.

Part 1: SAD (24-h Continuous IV Infusion)

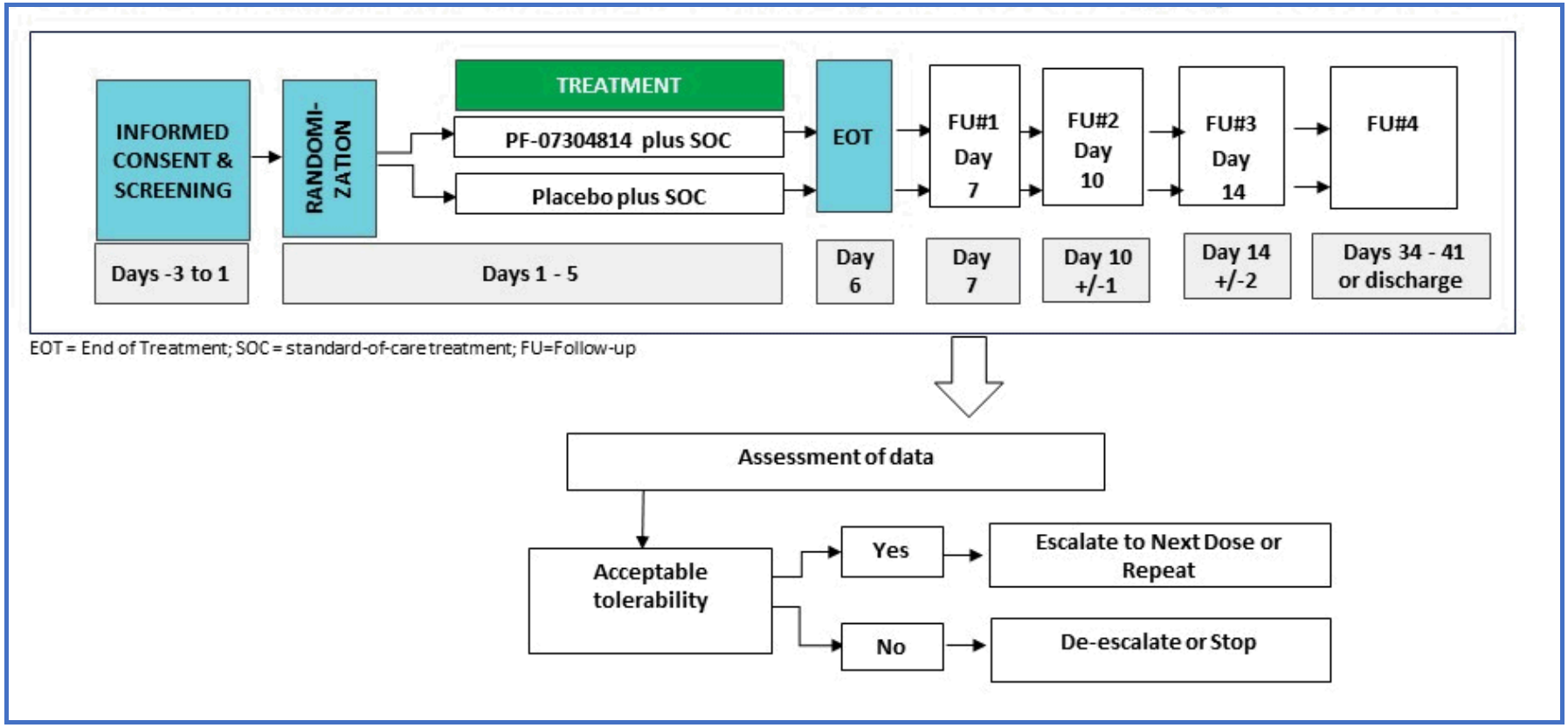


EOT = End of Treatment; SOC = standard-of-care treatment; FU= Follow-up



Precautionary **sentinel** dosing will be used in each dose-escalating cohort in Part 1. A small cohort of 2 participants (1 receiving PF-07304814 and 1 receiving placebo) will be dosed prior to the remainder of the cohort. All available safety and tolerability data from the 2 sentinel participants up to at least Day 3 at 24 hours post completion of dosing will be reviewed by the Investigator(s) (if available), the study team and IRC. The IRC will then determine whether it is safe to proceed to dose the remaining participants in the cohort.

Part 2: MAD (120h Continuous IV Infusion)



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.

PART 1: SAD (24-h infusion)

Visit Identifier	Screening Days -3 to 1	Day 1						End of Treatment Day 2	Follow-up 1 (Day 3)	Follow-up 2 (Day 6)[k] ±1 day Phone call where necessary	Follow-up 3 (Days 30-37)[k] Phone call where necessary	Early Termination
Planned Hours Post Start of Infusion		Pre-dose	0h	0.5h	2h	6h	12h	24h	48h			
ELIGIBILITY												
Informed consent	X											
Verify inclusion/exclusion criteria	X											
Demographics & Medical history	X											
Required Confinement		X	→	→	→	→	→	→	X			
PHYSICAL EXAMINATION & ECG & VITALS												
Complete physical examination	X							X				X
Targeted physical examination		X							X	X		
Supine Vital signs (temperature, pulse rate, blood pressure, respiratory rate)	X	X		X	X	X	X	X	X	X		X
Pulse oximetry/SpO_2	X	X						X	X	X		X
Weight, Height	X											
12-Lead ECG[a]	X	X				X[a]	X[a]	X[a]	X	X		X
ECG Telemetry[b]	X	X	X	→	→	→	X					

Visit Identifier	Screening Days -3 to 1	Day 1						End of Treatment Day 2	Follow-up 1 (Day 3)	Follow-up 2 (Day 6)[k] ±1 day Phone call where necessary	Follow-up 3 (Days 30-37)[k] Phone call where necessary	Early Termination
Planned Hours Post Start of Infusion		**Pre-dose**	**0h**	**0.5h**	**2h**	**6h**	**12h**	**24h**	**48h**			
LABORATORY												
Hematology[c]	X	X				X		X	X	X		X
Blood chemistry[c]	X	X				X		X	X	X		X
Coagulation Panel (PT, aPTT, D-dimer) and Fibrinogen		X				X		X	X	X		X
Urinalysis[c]	X	X				X		X	X	X		X
FSH (post-menopausal females only)[c]	X											
Pregnancy test (WOCBP only)	X[c,d]									X[d]		
CCI		[redacted]										
SARS-CoV-2 Viral load Assessments[e]	X	X				X		X	X	X		X
Plasma PD Biomarker Assessments[g]		X				X[f]		X	X	X		X
Serum PD Biomarker Assessments[h]		X				X[f]		X	X	X		X
Banked Biospecimen (Prep D1)		X				X[f]		X	X			X
Plasma Pharmacokinetics (PF-07304814 and PF-00835231)		X				X		X[i]	X			X
CCI		[redacted]						[redacted]				
Urine Pharmacokinetics [redacted] **(Cohort 2 only)**		X[j]	X	→	→	→	→	X **(36h)**				
RANDOMIZATION		X										
STUDY INTERVENTION												
Study intervention administration			X	→	→	→	→	X				
Infusion site assessment (as part of AE)			X	→	→	→	→	→	X	X	X	X
STUDY PROCEDURES & ASSESSMENTS												
CCI	[redacted]	[redacted]						[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Contraception check		X								X	X	X

Visit Identifier	Screening Days -3 to 1	Day 1						End of Treatment Day 2	Follow-up 1 (Day 3)	Follow-up 2 (Day 6)[k] ±1 day Phone call where necessary	Follow-up 3 (Days 30-37)[k] Phone call where necessary	Early Termination
Planned Hours Post Start of Infusion		**Pre-dose**	**0h**	**0.5h**	**2h**	**6h**	**12h**	**24h**	**48h**			
CONCOMITANT TREATMENT(S)												
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
SERIOUS AND NON-SERIOUS ADVERSE EVENT MONITORING	X	X	→	→	→	→	→	→	→	X	X	X

a. Single ECG at Screening; triplicate ECGs all other timepoints. ECG read locally, and provided to central reader for final study report. The nominal times to complete ECG assessments for 6 hr and 12 hr time points is approximately ±30 minutes and ±60 minutes respectively. The ECG assessments at 24 hr time point should be completed within 2 hours before the end of infusion. Once started, triplicate measurements should be completed within 20 minutes of start of the 1st reading.

b. Baseline telemetry must be captured at any time for at least 2 hours while the participant is awake between on Day -1 and pre-dose on Day 1.

c. Screening labs will be performed locally or onsite. Labs after Screening will be performed centrally with the exception of **pre-dose, 6h and 24h** on Day 1 which will be performed both locally and centrally.

d. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.

e. Specimens for SARS-CoV-2 RT-PCR testing for viral load will include nasopharyngeal swab and saliva samples.

f. Optional collections.

g. Plasma PD biomarker assessments may include cytokines of inflammatory response (eg, IL-1B, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13 TNF-α, and IFN-γ) and proteomics.

h. Serum PD biomarker assessments may include generalized endothelial damage/anemia (eg, ferritin), cardiac dysfunction (eg, CK, proBNPII, and troponin), general markers of sepsis/organ damage (eg, LDH, hsCRP, and cystatin-C), haptoglobin, and serological endpoints (anti-SARS CoV-2).

i. **PK samples on Day 2: 24h PK draw should be approximately within 30 min before end of infusion and then at 4 hours post end of infusion which corresponds to 28h.**

j. Administration starts on Day 1 and continues for 24 hours and ends on Day 2. **Sentinel dosing will be used in each dose-escalating cohort**. A small cohort of 2 participants (1 receiving PF-07304814 and 1 receiving placebo) will be dosed prior to the remainder of the cohort. All available safety and tolerability data from the 2 sentinel participants up to Day 3 at 24 hours post completion of dosing will be reviewed by the Investigator(s) (if available), the study team and IRC. The independent IRC will then determine whether it is safe to proceed to dose the remaining participants in the cohort.

k. For discharged participants, Days 6 and 30-37 should be conducted at the clinical site. However, if this is not possible, the visit may be conducted by phone in which case only clinical data (AE, CCI concomitant medications) and contraception check will be obtained. (If available, kits to assess viral load to be provided for at-home specimen collection in the instance that a visit is conducted by telephone, and arrangements may be made to collect blood samples for clinical chemistry and/or hematology).

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PART 2: MAD (120-h infusion)

Visit Identifier	Screening Days -3 to 1	Treatment Day Day 1	Treatment Days 2-5	End of Treatment Day 6	Follow-up 1 (Day 7)	Follow-up 2 (Day 10)[l] ±1 day	Follow-up 3 (Day 14)[l] ±2 days	Follow-up 4 (Day 34-41)[l]	Early Termination
Planned Hours Post Start of Infusion		**pre-Dose**	**24h (Day 2), 48h (Day 3), 72h (Day 4), 96h (Day 5)**	**120h**					
ELIGIBILITY									
Informed consent	X								
Verify inclusion/exclusion criteria[a]	X								
Demographics & Medical history	X								
Required Confinement		X	→	→	X				
PHYSICAL EXAMINATION & ECG & VITALS									
Complete physical examination	X			X					X
Targeted physical examination		X	X		X	X	X	X	
Supine vital signs (temperature, pulse rate, blood pressure, respiratory rate)	X	X	X	X	X	X	X	X	X
Pulse oximetry/SpO_2	X	X	X	X	X	X	X	X	X
Weight, Height	X								
12-Lead ECG[b]	X	X	Day 2, 3, 5 only	X	X	X	X	X	X
LABORATORY									
Hematology[c]	X	X	Day 2, 3, 5 only	X	X	X	X	X	X
Blood chemistry[c]	X	X[d]	Day 2, 3, 5 only	X[d]	X	X	X	X	X
Coagulation Panel (PT, aPTT, D-dimer) and Fibrinogen		X	Day 2, 3, 5 only	X	X	X	X	X	X
Urinalysis[c]	X	X	Day 3 only	X	X	X	X	X	X
FSH (to confirm post-menopausal status)	X								
Pregnancy test (WOCBP only)	X[c,e]						X		
CCI [redacted]									
SARS-CoV-2 Viral load Assessments[f]	X	X	Day 3 only	X	X	X	X	X	X
Plasma PD Biomarker Assessments[g]		X	Day 2, 3, 5 only	X	X	X	X	X	X
Serum PD Biomarker Assessments[h]		X	Day 2, 3, 5 only	X	X	X	X	X	X
Serum PD Biomarker - Serology[h]		X		X				X	
CCI [redacted]									

Visit Identifier	Screening Days -3 to 1	Treatment Day Day 1	Treatment Days 2-5	End of Treatment Day 6	Follow-up 1 (Day 7)	Follow-up 2 (Day 10)[l] ±1 day	Follow-up 3 (Day 14)[l] ±2 days	Follow-up 4 (Day 34-41)[l]	Early Termination
Planned Hours Post Start of Infusion		**pre-Dose**	**24h (Day 2), 48h (Day 3), 72h (Day 4), 96h (Day 5)**	**120h**					
Plasma Pharmacokinetics (PF-07304814 and PF-00835231)		X	Day 2, 3, 5 only	X[i]	X				X
CCI [redacted]		[redacted]		[redacted]					
RANDOMIZATION		X							
STUDY INTERVENTION									
Study intervention administration		X (after pre-dose assessments)	X	X					
Infusion site assessment		X (after infusion start)	X	→	X	X	X	X	X
STUDY PROCEDURES & ASSESSMENTS									
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]								
Contraception check[k]		X			X	X	X	X	X
CONCOMITANT TREATMENT(S)									
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
SERIOUS AND NON-SERIOUS ADVERSE EVENT MONITORING	X	→	→	→	→	→	→	X	X

a. Baseline SARS-CoV-PCR testing must have been performed within 72 hours prior to Screening.

b. Single ECG at Screening; triplicate ECGs at all other timepoints. ECG read locally and provided to central reader for final study report. Once started, triplicate measurements should be completed within 20 minutes of start of the 1st reading.

c. Screening labs will be performed locally or onsite. Labs for **pre-dose, Days 2, 3, and 5** will be performed both locally and centrally. Labs for EOT and follow-up visits (FU 1, FU 2, FU 3, and FU4), will be at central lab only.

d. 10-hour fasting required to include lipid panel as part of the blood chemistry.

e. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.

f. Specimens for SARS-CoV-2-PCR testing for viral load will include nasopharyngeal swab and saliva samples.

g. Plasma PD biomarker assessments may include cytokines of inflammatory response (eg, IL-1B, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, and IFN- γ) and proteomics.

h. Serum PD biomarker assessments may include generalized endothelial damage/anemia (eg, ferritin), cardiac dysfunction (eg, CK, proBNPII, and troponin), general markers of sepsis/organ damage (eg, LDH, hsCRP, and cystatin-C), haptoglobin, procalcitonin, and serological endpoints (anti-SARS CoV-2).

i. Blood sample collection **at approximately within 30 min before end of infusion (~120h),** and at **2 and 6 hours** post the end of the infusion, which correspond to approximately **122h and 126h** post the start of infusion. On days 2, 3, and 5, the nominal time of collections are 24h, 48h, and 96h respectively, but not within 30 minutes of infusion bag switch.

[redacted]

k. At time of early termination, or if discharged from hospital.

l. For discharged participants, Days 10, 14 and 34-41 should be conducted at the clinical site. However, if this is not possible, the visit may be conducted by phone in which case only clinical data (AE, CCI [redacted] concomitant medications) will be obtained (If available, kits to assess viral load to be provided for at-home specimen collection in the instance that a visit is conducted by telephone, and arrangements may be made to collect blood samples for clinical chemistry and/or hematology).

2. INTRODUCTION

PF-07304814 is a phosphate prodrug of PF-00835231, a potent and selective inhibitor of the SARS-CoV-2 3CL protease, that is being developed as a continuous IV infusion for the treatment of patients hospitalized with COVID-19.

2.1. Study Rationale

The current study is the first clinical administration with PF-07304814. It is designed as a 2-part study in hospitalized COVID-19 patients as a randomized, double-blind, sponsor-open, parallel group, placebo-controlled trial. Part 1 is to evaluate safety, tolerability, PK and markers of clinical activity of escalating doses of PF-07304814 given as 24-hour IV infusions. Part 2 is to evaluate safety, tolerability, PK and markers of clinical activity with escalating doses of PF-07304814 given as 120-hour IV infusions.

2.2. Background

Disease Overview

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 illness, 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 severe inflammation associated with elevations in pro-inflammatory cytokines, ARDS, acute cardiac injury, thromboembolic events, hypercoagulability, and/or kidney injury.[5-9]

Current Treatment Options

As of December 2020, vaccines are not yet widely available to prevent infection with SARS-CoV-2 and aside from symptomatic and/or supportive treatments there are few drugs approved and available to treat COVID-19. As of June, 2020, only 1 anti-viral drug with activity against SARS-CoV-2, Remdesivir, an RNA polymerase inhibitor, has shown clinical benefit in hospitalized patients with COVID-19.[10] While additional data from studies of Remdesivir and other drugs are becoming available, published preliminary reports suggest that Remdesivir may not be sufficient as monotherapy in all subsets of patients across the spectrum of disease.[10] Furthermore, Remdesivir is only available on a limited basis, through emergency use authorization in the US,[11] authorization for compassionate use in the EU,[12] and approved in a small number of countries.[13-15]

The FDA has issued EUA to 2 monoclonal antibodies, bamlanivimab and the combination casirivimab plus imdevimab, the drug baricitinab, in combination with remdesivir, and convalescent plasma for the treatment of COVID-19. The use of monoclonal antibodies is limited to the outpatient setting in patients at high risk of progressing to severe disease and/or hospitalization. At the time of the most recent update to the COVID-19 Treatment Guidelines Panel (03 December 2020), the Panel did not believe there was sufficient data to recommend any of these 4 therapeutics as part of the standard of care.

In addition, the glucocorticoid anti-inflammatory dexamethasone has been recommended in the COVID-19 Treatment Guidelines Panel at NIH guidelines for the treatment of on the basis of the preliminary report from the RECOVERY trial [DOI: 10.1056/NEJMoa2021436], for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated or who require supplemental oxygen [https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/corticosteroids/].

In spite of these advances, there remains an urgent need for additional safe and more effective therapeutic interventions that shorten time to clinical recovery and prevent the progression of infection to more severe disease and death. 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.

Rationale for Development of PF-07304814

The SARS 3CL protease is a virally encoded enzyme that is critical to the SARS-CoV-2 life cycle, analogous to other obligatory virally encoded proteases (eg, HIV Protease, HCV Protease).[16] Mutagenesis experiments with other coronaviruses and picornaviruses that are related to SARS-CoV-2 (picornavirus-like supercluster) have demonstrated that the activity of the 3CL protein (or the corresponding picornaviral 3C enzyme) is essential for viral replication. No close human analogs of the SARS 3CL enzyme are known, suggesting that appropriate SARS 3CL inhibitors may function as selective anti-SARS and other coronaviruses as therapeutic agents.

Inhibition of the SARS 3CL protease is a mechanism of action distinct from that of Remdesivir, which is a prodrug of an adenosine nucleoside analogue that interferes with SARS-CoV-2 RNA-dependent RNA polymerase. In vitro studies (see Section 2.2.1.1.1), indicate that the combination of PF-00835231, the active moiety of the phosphate prodrug of PF-07304814, and Remdesivir may have an additive effect with respect to inhibiting viral replication of SARS-CoV-2.

2.2.1. Non-clinical Overview

2.2.1.1. Non-clinical Pharmacology:

2.2.1.1.1. In vitro Pharmacology

PF-00835231 has been determined to be a potent and selective inhibitor of the SARS $3CL^{pro}$. PF-00835231 inhibited the full length enzyme activity of SARS-CoV-2 $3CL^{pro}$ with an IC_{50} of 0.00692 µM (Ki^{app} of 0.0003 µM), and the prodrug, PF-07304814 inhibited the same enzyme with an IC_{50} of 0.443 µM (Ki of 0.174 µM), indicating the active moiety PF-00835231 is >600-fold more active than the prodrug. PF-00835231 inhibited SARS-CoV-1 $3CL^{pro}$ with a Ki^{app} of 0.0047 µM and inhibited the HCoV-229E $3CL^{pro}$ with a Ki^{app} of 0.0012 µM.

For the PF-07304814 development program the antiviral activity of the active moiety, PF-00835231 and the prodrug, PF-07304814 were assessed in several in vitro SARS-CoV-2 assays within different laboratories as summarized in Table 1.

Table 1. Assay Conditions to Assess the Antiviral SARS-CoV-1 and SARS-CoV-2 Activity of PF-07304814 and PF-00835231

	Assay Location				
Assay Parameters	**NYU[a]**	**NYU[b]**	**SRI[c]**	**Rega[d]**	**Scripps[e]**
Virus strain	USA-WA1/2020	Washington	SARS-CoV-1 (Toronto 2); SARS-CoV-2 (USA-WA1/2020)	SARS-CoV-1 (200300592-Vietnam); SARS-CoV-2 (BetaCov GHB-03021/2020)	USA-WA1/2020
Cell type	A549-ACE2	Human primary HAE	VeroE6-ACE2 enriched	VeroE6-EGFP	HeLa-ACE2
Cell origin	Human lung	Human lung	Monkey kidney	Monkey kidney	Human cervical
Duration	24, 48 hours	24, 48 hours	3 days	5 days	24 hours
End point	Viral protein	Virus production	CPE	CPE	Viral protein
Detection	Immunofluor imaging	Plaque assay	CTG	Fluor imaging	Immunofluor imaging

a. Experiments conducted at New York University Langone School of Medicine.
b. Experiments conducted at New York University Langone School of Medicine.
c. Experiments conducted at Southern Research Institute in Birmingham, Alabama.
d. Experiments conducted at Rega Institute, Leuven, Belgium.
e. Experiments conducted at Scripps Research Institute.

These assays are representative of the current antiviral assessments being used in the field to date. The antiviral activities in the physiologically relevant human lung derived cell line, A549-ACE2 with a direct viral readout were used as an approximation for C_{eff} selection purposes. The antiviral activity of PF-00835231 and Remdesivir (as a control) were evaluated against SARS-CoV-2 A549-ACE2 cells as summarized in Table 2.

Table 2. Summary of PF-00835231 and Remdesivir Inhibition of SARS-CoV-2 Expression in A549-ACE2 Cells

Time post infection	EC_{50} µM[a] (95% CI)	EC_{90} µM[a] (95% CI)	CC_{50} µM[a] (95% CI)	TI[b]
	PF-00835231			
24 Hours	0.221 (0.137 to 0.356)	0.734 (0.391 to 1.38)	>10 (ND)	>46
48 Hours	0.158 (0.079 to 0.314)	0.439 (0.380 to 0.508)	>10 (ND)	>65
	Remdesivir			
24 Hours	0.442 (0.240 to 0.814)	1.19 (0.622 to 2.28)	>10 (ND)	>23
48 Hours	0.238 (0.122 to 0.463)	0.592 (0.534 to 0.656)	>10 (ND)	>43

a. Value is the geometric mean (n=3).
b. TI calculated as: CC_{50}/EC_{50}.

The inhibitory activity of PF-00835231 on SARS-CoV-2 in A549-ACE2 cells was confirmed by data from polarized human airway epithelial (HAE) cells. PF-00835231 maintains the potent inhibition of SARS-CoV-2 virus production at 0.025, 0.5, and 10 µM from various time points with the most significant reduction of 8-, 30- and 2940-fold, respectively, at 48 hours post-infection (data not shown) with similar results for Remdesivir, tested in parallel as a control. These preliminary results provide an indication that the compound activity in this model is similar to what was observed for the A549-ACE2 assay.

The anti-SARS-CoV-2 activity of PF-00835231 was supported by data from another human cell line albeit of a different organ origin. In HeLa-ACE2 cells, PF-00835231 inhibited SARS CoV2 replication at an average EC_{50}/EC_{90} of 0.144 µM/0.398 µM, in line with results in A549-ACE2 cells (Table 3).

Table 3. PF-00835231 and Remdesivir inhibition of SARS CoV2 expression in HeLa-ACE2 cells

EC_{50} µM (95% CI)	EC_{90} µM (95% CI)
PF-00835231[a]	
0.144 (0.074 to 0.278)	0.398 (0.143 to 1.10)
Remdesivir[b]	
0.074 (0.063 to 0.087)	0.168 (0.108 to 0.250)

n = number of replicates.
a. Values are the geometric mean (n=3).
b. Values are the geometric mean (n=4).

In addition, for comparative purposes we generated efficacy data in VeroE6 cells as SARS antiviral assays are typically performed in Vero cells which support high levels of SARS replication. However, they are not considered as relevant as A549-ACE2 due to the fact they are not of human origin (African green monkey) as well as derived from a different organ type (kidney). In addition, contrary to the virus target cells in lung and bronchus, Vero cells are known to express high levels of P-gp, a multi-drug resistance protein that pumps xenobiotics out of cells.[17] Since PF-00835231 is a P-gp substrate, anti-viral screening in this cell type was done with and without the presence of a P-gp EI, CP-100356. The levels of P-gp expression in the cells used in SARS-CoV-2 antiviral assays were analyzed. P-gp was shown to be expressed to much higher levels (>380 fold) in Vero76, VeroE6, VeroE6 enriched for hACE2, VeroE6 stably expressing EGFP than the physiologically relevant A549 cells as well as HeLa cells. Data from different labs using Vero cells showed that PF-00835231 alone had significantly higher EC_{50} values than in the presence of 0.5 µM EI. This observation of PF-00835231 inhibition was reproduceable in tests using VeroE6 cells or VeroE6 cells expressing EGFP. Furthermore, increasing the concentration of the EI from 0.5 to 2 µM when P-gp activity appears sufficiently suppressed, EC_{50} levels in VeroE6 cells are at the similar level as in A549 cells (Table 4).

Table 4. Summary of the In Vitro Antiviral Activity, Cytotoxicity, and TI for PF-00835231 With and Without the P-gp Efflux Inhibitor, CP-100356

Virus Strain	Host Cell	PF-00835231 ± EI	EC50 µM			CC50 µM		TI[a]
			Geometric Mean	(95% CI)	n	Geometric Mean	n	
SARS-CoV-2	VeroE6[b]	- EI (0 µM)	88.9[c]	76.8 to 103	5	>100[c]	8	>1.2
		+ EI (0.5 µM)	8.21[c]	3.12 to 21.6	8	>100[c]	8	>21
		+ EI (2 µM)	0.760[c]	0.449 to 1.29	4	>50[c]	4	>32
	VeroE6[d]	- EI (0 µM)	39.8[c]	29.8 to 53.2	10	>100	9	>2.5
		+ EI (0.5 µM)	2.93[c]	1.13 to 7.64	7	>100	6	>35
		+ EI (2 µM)	0.236[c]	0.135 to 0.412	6	>100	6	>400
SARS-CoV-1	Vero76[e]	- EI (0 µM)	5.0	3.1 to 8.1	4	≥208[f]	5	>42
		+ EI (0.5 µM)	0.11	ND	2	>100	2	>900
	VeroE6[g]	- EI (0 µM)	>100	ND	6	>100	6	ND
		+ EI (0.5 µM)	10.8[c]	3.80 to 30.8	6	>100	6	>11
	VeroE6[h]	- EI (0 µM)	93.8[c]	ND	1	>100	2	>1.1
		+ EI (0.5 µM)	1.91[c]	0.701 and 5.18[i]	2	>100	2	>45
HCoV-229E[j]	MRC-5	- EI (0 µM)	0.088	0.047 to 0.160	16	≥208[f]	6	≥2300
		+ EI (0.5 µM)	0.19	ND	1	>1	1	>5.3

	MRC-5	- EI (0 µM)	0.0692	0.0561 to 0.0852	7	>100	5	>510
		+ EI (0.5 µM)	0.0795	0.0169 to 0.373	3	>100	3	>770
	Huh7	- EI (0 µM)	0.0909	0.0638 to 0.129	4	>100	4	>480
		+ EI (0.5 µM)	0.0778	0.0316 to 0.192	3	>100	3	>1300

a. The TI was calculated by dividing CC_{50}/EC_{50}.
b. SARS-CoV-2 (EPI ISL 407976|2020-02-03/BetaCoV/Belgium/ GHB03021/2020) strain.
c. EC_{50} curves were fit to a Hill slope of 3. If cytotoxicity was detected at >30% effect, the corresponding concentration data was eliminated for the determination of EC_{50}.
d. SARS-CoV-2 (USA_WAI/2020_TVP23156) strain.
e. SARS-CoV-1 Toronto 2 strain.
f. PF-00835231 solubility in assay media, pH 6.5 was 208 uM.
g. SARS-CoV-1 (200300592-Vietnam).
h. SARS-CoV-1 Toronto 2 strain.
i. Values listed are the 2 values (when n=2); not the CI.
j. HCoV-229E is ATCC strain.

The antiviral activity data of PF-00835231 against SARS-CoV-2 in the various tested cell lines of different origins are consistent, including in the unrelated monkey kidney derived Vero cells when its P-gp activity was sufficiently suppressed. The EC_{50} value of ~0.25 µM and EC_{90} value of ~0.5 µM derived from the physiologically relevant A549-ACE2 human lung carcinoma cells are supported by data from other cell lines, demonstrating a consistent intrinsic potency against SARS-CoV-2.

To understand the activity of PF-00835231 against other coronaviruses in human cell lines (normal human lung epithelial cells [MRC-5] and human hepatocellular carcinoma cells [Huh7]), the compound was tested for antiviral activity against an alpha coronavirus, HCoV-229E, which naturally circulates among humans. Anti-viral activity was observed with the compound potently inhibiting HCoV-229E-induced cytopathic effects in both cell lines, demonstrating EC_{50} values ranging from 0.069 to 0.190 µM regardless of the presence of the EI (Table 4). In contrast to Vero cell assays, the presence of an EI did not enhance PF-00835231 activity, consistent with the known lack of P-gp activity in MRC-5 cells.[18]

PF-00835231 binds to the active site of both SARS-CoV-1 and SARS-CoV-2 $3CL^{pros}$, as determined by X-ray co-crystal structures. Both structures are consistent with a covalent and reversible interaction of PF-00835231 at the active site catalytic cysteine residue of each $3CL^{pro}$, thus inhibiting the activity of the protease. PF-00835231 was also determined to be active against several other human coronavirus $3CL^{pro}$, including that of MERS, HCoV-OC43, HCoV-HKU1, and HCoV-NL63. This pan-coronavirus $3CL^{pro}$ inhibition could be explained by the similarity of $3CL^{pro}$ across the Coronaviridae family where critical amino acid residues involved in enzyme-inhibitor binding interactions are particularly well conserved. For example, PF-00835231 interacts only with the side chains of coronavirus $3CL^{pro}$ amino acids that are completely conserved between SARS-CoV-1 and SARS-CoV-2.

Further details may be found in the IB.

2.2.1.1.2. In vivo Pharmacology

Studies on in vivo pharmacology of PF-07304814 or PF-00835231 have not been reported. However, some in vivo model studies have been completed the in-life phase and a preliminary analysis is shown below.

The mouse is not a natural host of SARS-CoV-2 or CoV-1. Although mice have the ACE2 receptor, it is sufficiently different from the human version of ACE2 such that the viruses are unable to infect mice. However, by passage of SARS-CoV-1 virus multiple times in mice, the virus Spike (S) protein adapts to enable utilization of the mouse receptor. Mutations were present in 3CL protease coding sequence of the mouse-adapted CoV-1 strain, but they were distant from the active site which is 100% identical between CoV-1 and CoV-2. The resulting virus can infect mice and cause disease, which is characterized by weight loss and lung pathology that are consistent with human disease. The virus also replicates to high levels in the lungs of the mice. This mouse-adapted model of CoV-1 infection was used to evaluate PF-00835231 (the parent molecule to the prodrug, PF-07304814). The experiments are on-going. To summarize, mice that were infected with mouse-adapted CoV-1 were

treated with PF-00835231 at 100 mg/kg, twice daily (BID) by the SC route. This is a dose that was predicted to give an exposure of the drug at C_{min} of approximately 500 nM or about EC_{90}. In one experiment, treatment was initiated at the time of infection (Day 0) or delayed for 1- or 2-days post-infection. Viral titers in the lung were reduced ~2.0, 1.5 and 1.0 log_{10} with treatment starting on Days 0, 1, and 2 post-infection, respectively. Weight loss and histopathologic signs of disease were decreased, particularly when dosing of PF-00835231 was started on Day 0. In a second experiment, treatment with PF-00835231 was initiated on Day 0 and the dose of drug was varied (30, 100, 300 mg/kg, BID, SC). A dose-dependent decline in viral titers in the lung was observed for the three doses: ~1.5 log_{10} at 30 mg/kg; ~3 log_{10} at 100 mg/kg; and ≥3.5 log_{10} at 300 mg/kg. The decline in weight loss caused by the virus was reduced by treatment with PF-00835231 at all doses compared to infected, untreated mice. The drug exposure at 300 mg/kg in this experiment was 3-4-fold higher than that observed previously with 100 mg/kg. Histopathology for this experiment is not available currently.

2.2.1.2. Nonclinical Pharmacokinetics and Metabolism

2.2.1.2.1. Nonclinical Pharmacokinetics and Prediction of Human Pharmacokinetics

Preliminary human in vitro metabolism data indicate PF-07304814 is rapidly metabolized by alkaline phosphatase in the liver forming the active metabolite PF-00835231. Both PF-07304814 and PF-00835231 exhibit similar metabolic profiles in rat, dog, monkey and human liver microsomes with no human specific metabolites observed.

Overall, based on human vitro and animal in vivo data the major clearance pathway for PF-00835231 is predicted to be via CYP3A4 metabolism (fm 0.76) with minor contributions from additional CYPs (fm 0.12) and via renal clearance (fm 0.12).

Preliminary assessments based on in vitro DDI studies and the predicted systemic exposure in humans following the projected efficacious dose indicate a low potential for DDI due to PF-07304814 or PF-00835231 mediated inhibition of CYP1A2, 2B6, 2C19, 2C8, 2C9, 2D6 and CYP3A4. PF-00835231 demonstrated weak time-dependent inhibition of CYP3A.

There are potential DDI risks of PF-00835231 as a substrate when co-administered with strong inhibitors and inducers of CYP3A4. Preliminary SimCYP modeling indicated an approximate 2× or 0.5× change in PF-00835231 AUC when co-administered with a strong CYP3A4 inhibitor (eg, itraconazole) or strong inducer (eg, rifampin), respectively. At the predicted target C_{eff} (Section 2.2.1.2.2) exposure, PF-07304814 and PF-00835231 have a low potential as a perpetrator for enzymatic or transporter based DDIs. As higher doses are explored (ie, 10× the C_{eff}), PF-00835231 has the potential to time-dependently inhibit CYP3A (up to 3× AUC increase using midazolam as a probe substrate), and a potential for a transporter DDI by inhibition of P-gp, BCRP, OATP1B1/1B3, OCT1, and MATE1/2K.

In humans the predicted CL_p of PF-07304814 is ~10 mL/min/kg, Vd_{ss} of 0.1 L/Kg and effective $t_{½}$ ~0.1 hour and the predicted CL_p and V_{ss} of PF-00835231 are 6 mL/min/kg and 1 L/kg respectively, providing an effective $t_{½}$ of approximately 2 hours.

Further details may be found in the IB.

2.2.1.2.2. Pharmacokinetics-Pharmacodynamics Relationship

Based on experience with antiviral agents, PF-00835231 is expected to exhibit anti-SARS-CoV-2 activity in humans, when the free plasma exposure is maintained at or above the in vitro EC_{90} under a continuous infusion dosing regimen. Due to steep exposure-response curve in the in vitro antiviral potency data, only a 2 to 3-fold difference in concentration was observed between the EC_{50} and EC_{90} antiviral potencies in each assay.

PF-00835231 was assayed in a range of antiviral in vitro assays, which include different cell types (different variants of VeroE6 cells, HELA cells, human airway epithelial cells and human epithelial lung carcinoma cells), different assay times (24 hours – 7 days), different assay endpoints (cell viability, viral replication, plaque) and different virus strains (SARS-CoV-2-Washington strain, SARS-CoV-2-BetaCov GHB-03021/2020). The predicted target C_{eff} is 0.5 µM free based on the most physiologically relevant cell types: EC_{90} ~ 0.44 µM free (n=3) in the human lung carcinoma, confirmed by the anti-viral time course experiment done in the human airway epithelial model (preliminary data indicates unbound EC_{90}<0.5 µM). Although in vitro anti-viral activity has been observed for the prodrug PF-07304814 this is likely to be due to the partial conversion to its active moiety in the assay and therefore only antiviral activity for PF-00835231 has been considered for the target C_{eff} and dose estimates.

2.2.1.3. Non-clinical Safety

The toxicity profile of PF-07304814 was assessed in GLP continuous IV infusion studies for up to 14 days in rats and cynomolgus monkeys. In both studies, animals were administered control or PF-07304814 at doses of 70, 360, and 1000 mg/kg/day as a continuous IV infusion.

PF-07304814 and PF-00835231 were tolerated and without test article related effects in rats up to 1000 mg/kg for up to 14-day of continuous infusion. CCI

[redacted]

[redacted]

CCI

[redacted]

The free plasma exposure at the highest tolerated dose (360 mg/kg/day) were $C_{max,\ free}$ of 3.92 µg/mL on Day 14 and $AUC_{24,\ free}$ of 71.9 µg•h/mL on Day 1 for PF-00835231 (active moiety), and $C_{max,\ free}$ of 1.79 µg/mL on Day 14 and $AUC_{24,\ free}$ of 30.4 µg•h/mL on Day 1 of PF-07304814 (prodrug). They were 16x and 13x the predicted human unbound C_{max} and AUC_{24}, respectively, for the active moiety PF-00835231, at the projected human efficacious dose.CCI

[redacted]

PF-07304814 and PF-00835231 were negative in the in vitro bacterial reverse mutation assay and did not induce micronuclei formation in vitro. Both compounds had minimal potential for secondary (off-target) pharmacology at clinically relevant exposures, and neither compound inhibited hERG current amplitude at up to 300 µM. Both compounds were compatible with human blood.

The nonclinical safety profile of PF-07304814 has been adequately characterized to support continued clinical development. Further details may be found in the IB.

2.2.2. Clinical Overview

C4611001 is the first clinical study using PF-07304814, and is designed to establish PK, safety and tolerability in a hospitalized COVID-19 population. In order to evaluate these parameters in a more homogeneous healthy population, an additional Phase 1 study, C4611007, is initiated and ongoing. Following the establishment of PK, safety and

tolerability of 24h and 120h infusions of PF-07304814 in these populations, the sponsor proposes a Phase 2/3 adaptive design efficacy study in hospitalized COVID-19 patients (C4611002).

As of 18 November, 2020, 4 patient participants in Cohort 1 received a single dose of PF-07304814 or placebo, administered as a 24-hour continuous IV infusion in the study C4611001. Based on emerging PK data in participants who received PF-07304814, dosing in Cohort 1 (500 mg dose) was stopped and dosing in a new cohort, Cohort 3, at 250 mg was initiated. As of 16 December, 2020, three participants in Cohort 3 have been dosed with either PF-07304814 or placebo.

2.2.2.1. Study C4611007 - Ongoing

This is the second clinical administration with PF-07304814, but first in healthy adult participants. This is a Phase 1, randomized, double-blind, sponsor open (ie, participant blind, investigator blind and sponsor open), placebo-controlled SAD study, with ongoing review of safety, tolerability, and PK.

There are 2 interleaving cohorts with a total of approximately 16 participants (approximately 8 participants in each cohort), with 2-period cross-over in each cohort. For each period, approximately 6 participants will have received a single dose of PF-07304814 administered as a 24h continuous IV infusion, and approximately 2 participants will have received placebo. Each participant may have received either a single dose of PF-07304814 or a placebo during each period.

The nominal doses of PF-07304814 are 50 mg, 150 mg, 500 mg, and 700 mg for a 24h continuous infusion. In addition to standard safety assessments, hsCRP, D-dimer, and coagulation panel (aPTT, PTT) are monitored to evaluate any potential pro-inflammatory or hypercoagulable effect of study intervention.

The study began in October 2020, and at the time of the data cutoff date 21 November 2020, safety data from last planned safety labs (Day 5) from the last participant was reviewed. There were 20 TEAEs reported by 12 participants. All of the TEAEs were categorized as mild in severity. One AE of injection site pain, reported as mild in severity, was considered treatment related by the investigator. For the description of each AEs please refer to the IB (December 2020). There were no deaths, serious AEs (SAEs), severe AEs, or discontinuations due to AEs during the study.

There were no individual laboratory abnormalities assessed as clinically significant by the investigator. Across the treatment groups there were no clinically significant changes in the inflammatory marker, hs-CRP. Tests evaluating the coagulation system, aPTT, PT, fibrinogen and D-dimer, were similarly without clinically significant changes over time. No participant developed a value that was clinically significantly elevated or outside the normal range. Overall, there was no evidence of a pro-inflammatory effect clinically or based on laboratory results, at all dose levels.

Preliminary pharmacokinetic (PK) data following single dose 24h continuous IV infusion at 50, 150, 500 and 700 mg are included in this update with a data cut-off date of 21 November 2020.

Maximum or near maximum plasma concentrations of the active moiety PF-00835231 were generally first observed ~6h post start of the infusion and sustained until the end of the infusion. PF-00835231 plasma concentrations declined rapidly afterwards. The $t_{½}$ values were only reportable at 500 and 700 mg and were 2.25 hour and 2.02 hour, respectively. Mean C_{max} and AUC values appeared to increase in a dose proportional manner in the dose range tested.

Maximum or near maximum plasma concentrations of the phosphate prodrug PF-07304814 were generally first observed ~3h and sustained until at least 16h post start of the infusion. Despite continuous infusion of the prodrug and sustained plasma concentration of the active moiety, the concentration of PF-07304814 declined before the end of the infusion. The $t_{½}$ values could not be determined since all plasma samples collected after the 16h post start of the infusion were BLQs of 40 ng/mL. While the mean C_{max} values appeared to increase in a dose proportional manner in the dose range tested, the AUC values appeared to increase in a slightly greater than dose proportional manner.

More detailed information may be found in the latest IB (December, 2020).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07304814 may be found in the latest IB (December, 2020), 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-07304814		
Potential risks associated with PF-07304814 include inflammatory effects, noted by changes in peripheral blood WBCs, CCI [redacted] and thrombo-emboli at the infusion site and/or in different tissues.	CCI [redacted]	Infusion duration limited to 5 days. Exposure limited by agreement with regulatory authorities. Close observation of AEs, vital signs, ECGs and laboratory assessments. In addition to the standard safety laboratory assessments, monitoring of markers of inflammation and coagulation (including hsCRP and LDH) will be performed. Participants with history of thrombotic events will be excluded (Exclusion criterion #6). Female participants on hormonal therapy will be excluded.
Study Procedures		
Peripheral intravenous catheterization (eg, for administration of the study intervention).	Intravenous catheterization may cause pain at the site of insertion, bruising, hematoma formation, bleeding, extravasation, and possibly infection at the catheter site or bloodstream infection.	Aseptic technique for both catheter insertion and study blood draws may mitigate the risk of infection. Other adverse effects can be managed via local care (eg, applying pressure to the site to stop bleeding) and/or analgesia. Faintness is typically transient and can be managed by placing the participant in a prone position with elevation of his/her legs.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Central venous catheterization or midline use for blood draws (not required by the protocol).	Central venous catheterization or midline, although not required by the protocol, may be indicated in some cases according to local standard of care and may lead to increased risk of DVT in some patients. As of 16-Oct-2020, 2 participants in sentinel dosing group of Cohort 1 experienced DVT in the arm where a midline was inserted. One participant received the study drug PF-07304814 and the other received placebo. The placebo and study drug were not infused through the midline.	Appropriate anti-coagulant prophylaxis administration should be considered as per local guidelines.
Potential for increased risk of intravenous infusion site reaction.	There may be potential risk of infusion site reaction due to low pH of study intervention and/or need for continuous intravenous infusion. - These risks are described in the SRSD for PF-07304814.	Monitoring of infusion site reactions will be performed through targeted PE and collection of AEs, which will be reviewed on an ongoing basis. Infusion solution may be diluted.
Other		
Not applicable.		

2.3.2. Benefit Assessment

Since this is the first clinical study of PF-07304814 the clinical benefit is unknown. The phosphate prodrug PF-07304814 is not expected to be active against the SARS 3CL protease. PF-00835231 (active moiety) has been shown to have SARS-CoV-2 antiviral activity in vitro, and it is intended to reduce virus titers and thereby reduce disease severity and risk of mortality in SARS-CoV-2 infected patients. Participants in this study therefore have the potential to benefit from PF-07304814 administration, however the benefit is unproven.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to participants in this study, the potential risks identified in association with PF-07304814 are justified by the potential anticipated benefits that may be afforded to hospitalized participants with SARS-CoV-2 infection.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To assess the safety and tolerability following single and multiple ascending doses of PF-07304814 in hospitalized participants with COVID-19.	N/A	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs (including infusion site reactions). • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements, pulse oximetry/SpO_2, and 12-lead ECG parameters.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the plasma PK of PF-07304814 and PF-00835231 and urinary PK of PF-00835231 following single ascending and multiple ascending dosesin hospitalized participants with COVID-19.	N/A	**Part 1: SAD** • PF-07304814 (prodrug) and PF-00835231 (active moiety) plasma PK: C_{24} (end of infusion) and C_{24} (dn). • PF-00835231 urinary PK parameters: Ae, Ae%. **Part 2: MAD** • PF-07304814 (prodrug) and PF-00835231 (active moiety) plasma PK: C_{120} (end of infusion), C_{max}, C_{ss}, and $t_{½}$.
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
[redacted]	C Cl	[redacted]
• Measurement of	N/A	• SARS-CoV-2 viral load (RT-PCR) and, if

Objectives	Estimands	Endpoints
SARS-CoV-2 viral load (by RT-PCR) and, if feasible, molecular analysis in nasopharyngeal swab and saliva samples over time.		feasible, molecular analysis in nasopharyngeal swab and saliva (at Screening, Days 1, 2, 3 and 6 for **Part 1: SAD**, and at Screening, Days 1, 3, 6, 7, 10, 14 and last follow-up for **Part 2: MAD**.
• Measurement of exploratory biomarkers.	N/A	• Change from baseline in biomarkers (on Days 1, 2, 3 and 6 for **Part 1: SAD**, and Days 1, 3, 6, 7, 10, 14 and last follow-up for **Part 2: MAD** may include: • Cytokines of inflammatory response (eg, IL-1B, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, and IFN-γ); • Coagulation (eg, PT, aPTT, D-dimer), fibrinogen and haptoglobin; • Generalized endothelial damage/anemia (eg, ferritin); • Cardiac dysfunction (eg, CK, proBNPII, and troponin); • General markers of sepsis/organ damage (eg, LDH, hsCRP, and cystatin-C), procalcitonin; • Serological endpoints: anti-SARS CoV-2; [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a First-In-Human Phase 1b study to evaluate the safety, tolerability and PK of PF-07304814 in participants who are hospitalized for treatment of COVID-19. The participants will be receiving SoC therapy for the treatment of mild, moderate, or severe COVID-19, but will not be eligible if they require mechanical ventilation or ECMO at screening or baseline. All participants will have a confirmed positive test for SARS-CoV-2 (see Section 5.1 for additional details) and onset of symptoms within 15 days of Screening. For inclusion into **Part 2: MAD** of the study, participants will be required to have had a positive test for SARS-CoV-2 (See Section 5.1 for details) within 72 hours prior to Screening.

This is a 2-part study in which up to a total of approximately 72 participants on SoC with the intervention such that approximately 72 evaluable participants complete the study. It is a randomized, double-blind, sponsor-open, parallel group, placebo-controlled trial.
Part 1: SAD is to evaluate safety, tolerability, and PK of escalating doses of PF-07304814 given as 24-hour IV infusions. Two planned and 3 optional cohorts with 8 participants/cohort will be included in **Part 1. Part 2: MAD** is to evaluate safety, tolerability, and PK of multiple ascending doses of PF-07304814 given as 120-hour IV infusions. Two planned and 2 optional cohorts with 8 participants/cohort will be included in **Part 2**.

4.1.1. Part 1: SAD

Precautionary **sentinel** dosing will be used in each dose-escalating, ie, increasing dose, cohort in **Part 1**. A small cohort of 2 participants (1 receiving PF-07304814 and 1 receiving placebo) will be dosed prior to the remainder of the cohort. All available safety and tolerability data from the 2 sentinel participants up to at least Day 3 at 24 hours post completion of dosing will be reviewed by the Investigator(s) (if available), the study team and IRC. The independent IRC will then determine whether it is safe to proceed to dose the remaining participants in the cohort.

Cohorts of 8 participants each who meet the eligibility criteria (see Sections 5.1 and 5.2) will be enrolled. The 2 sentinel participants will be randomized in a ratio of 1 (PF-07304814): 1 (placebo), while the remaining 6 participants will be randomized in a ratio of 5 (PF-07304814):1 (placebo). Both treatments will be administered in a telemetered (for 12 hours post the start of dosing) setting as a continuous IV infusion for 24 hours for each dose, in addition to SoC therapy.

All participants will follow the study procedures as outlined in Section 1.3, SoA. They will be required to stay in hospital from at a minimum, Day 1, pre-dose (at least 2 hours) through completion of Day 3 evaluations (Follow-up 1). Participants will then return for Day 6 (Follow-up 2) activities and a planned final follow-up visit per the SoA on Day 30-37 (Follow-up 3) for a total of approximately 4-5 weeks study participation from first dose to follow-up, excluding screening.

Participants who discontinue for reasons other than drug-related safety events during the trial may be replaced at the discretion of the Sponsor and investigator.

Three optional cohorts may be added to further explore the dose range based on emerging safety, tolerability and PK assessments. However, the projected exposures at the top dose (adjusted based on observed PK) in **Part 1: SAD** will not exceed the exposure limits agreed with competent regulatory authorities.

After reviewing emerging safety, tolerability, and PK data (Section 6.6.1) by the study team, the Investigator(s) (if available) and IRC, the decision to proceed to the next dose level will be made.

4.1.2. Part 2: MAD

Progression to **Part 2** will occur if safety, tolerability, and PK data from the **Part 1** 24-h infusion cohorts as well as those from study C4611007 are determined to be supportive and acceptable by competent regulatory authorities. The dose progression will be based on emerging PK, safety and tolerability data and will not exceed the exposure limits agreed with competent authorities.

Cohorts of 8 participants each who meet the eligibility criteria (see Sections 5.1 and 5.2) will be enrolled and randomized in a ratio of 6 PF-07304814:2 placebo. All participants will follow the study procedures as outlined in SoA. They will be required to stay in hospital from at a minimum, Day 1, pre-dose through completion of Day 7 evaluations (Follow-up 1). Participants will then return for Day 10 (Follow-up 2) and Day 14 (Follow-up 3) activities and a final planned follow-up (Follow-up 4) visit per the SoA on Days 34-41 for a total of approximately 5-6 weeks study participation from the start of dosing to follow-up, excluding screening.

Participants who discontinue for reasons other than drug-related safety events during the trial may be replaced at the discretion of the Sponsor and investigator.

4.2. Scientific Rationale for Study Design

This study will provide data on safety, tolerability, PK, biomarker changes and measures of disease activity in hospitalized patients infected with SARS-CoV-2. Since this is a first in human study, patients who require mechanical ventilation or suffer from severe, uncontrolled co-morbidities will be excluded to balance potential risk versus benefit. Risk is further mitigated by a single dose escalation design in **Part 1: SAD**, with extensive assessment of safety and PK. Precautionary **sentinel** dosing will also be used in each dose-escalating cohort in **Part 1**. A small cohort of 2 participants (1 receiving PF-07304814 and 1 receiving placebo) will be dosed prior to the remainder of the cohort. An independent IRC will assess whether it is safe to proceed to continued dosing within a cohort following sentinel dosing or whether it is safe to dose-escalate to the next dose level. In **Part 2**, PF-07304814 will be administered for a period of 5 days of continuous infusion at a dose based on emerging data and with the agreement of the competent regulatory authority. The potential for PF-07304814

to have beneficial antiviral activity will be explored by measurement of viral load, biomarkers of disease and assessment of disease progression on CCI [redacted]

The clinical benefit of PF-07304814 is unproven, and therefore to ensure all participants get the best care for COVID-19 study intervention will be administered in addition to SoC.

Studies to evaluate the development toxicity of PF-07304814 have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4: Contraceptive Guidance).

In addition to clinical safety and PK data, biofluids will be collected for virology and PD exploratory biomarker assessments at various times per schedule of assessments. In brief, nasopharyngeal swab and saliva samples will be collected for viral load assessments, and where feasible, viral genetic analysis. Emerging reports have suggested that COVID-19 patients can exhibit abnormal innate and adaptive immune responses to SARS CoV-2 infection.[20] As a result, immunological biomarkers (eg, monocyte profiles, interferon gamma, C-reactive protein, tumor necrosis factor, IL-6 and IL-8) will be assessed in blood. Serological endpoints will be examined as well. Literature reports also suggest a significant percentage of patients exhibit endothelial dysfunction and coagulation and specific organ vulnerabilities.[21,22] Blood will also be collected to examine coagulation endpoints (eg, D-dimer, and ferritin) and other specific organ damage endpoints (eg, cardiac troponin, etc).

CCI [redacted]

4.3. Justification for Dose

Doses presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data.

4.3.1. Rationale for Dose Selection

The approach for dose selection for this study includes consideration of all relevant information obtained in non-clinical pharmacology and toxicity studies with PF-07304814 or PF-00835231 (active moiety). Similar to other antiviral therapies, PF-00835231, the active moiety of the phosphate prodrug PF-07304814, is expected to exhibit therapeutic anti-SARS-CoV-2 activity in patients when the free plasma exposure is maintained at or above the in vitro EC_{90} values.[23-25]

4.3.2. Starting Dose and Dose Escalation in Part 1: SAD

This is a study in COVID-19 patients who are on SoC. To maximize the potential benefit of an anti-viral agent, the planned starting dose of PF-07304814 is to maintain a free plasma concentrations (C_{ss}) of PF-00835231 (active moiety) around EC_{90} of 0.5 µM (or a total plasma concentration of 0.526 µg/mL) according to in vitro pharmacology studies (Section 2.2.1.2.2).

Based on the predicted human PK parameters (Section 2.2.1.2.1), at a dose of 500 mg of PF-07304814 administered over 24-hour as a continuous infusion, the projected PF-00835231 (active moiety) C_{ss} is 0.53 µg/mL and the AUC_{24} is 11.2 µg•h/mL, CCI [redacted] (Section 2.2.1.3). At this dose, the projected PF-07304814 exposures (C_{ss} and AUC_{24}) provide at least 2.5-fold safety margins relative to the PK stopping limits (Section 2.2.1.3).

As of 18 November 2020, 4 patient participants received a single dose of 500 mg PF-07304814 or placebo administered as a 24-hour continuous IV infusion in study C4611001. While the preliminary safety profiles were acceptable, the exposures achieved at 500 mg in C4611001 were ~2-fold of initial PK stopping limits based on preliminary results in a limited number of patients who received active treatment. As such, the enrolment to Cohort 1 at 500 mg was stopped and a new cohort (Cohort 3) at 250 mg is open to enrolment.

If dose progression is further explored in **Part 1** of the study, the predicted exposures for both PF-00835231 and PF-07304814 will not exceed the agreed PK stopping limit with competent regulatory authorities.

4.3.3. Starting Dose and Dose Selection in Part 2: MAD

The starting dose of Part 2 is determined to be 5 daily doses of 250 mg via continuous infusion after careful review of all available safety and PK data from Part 1: SAD of study C4611001 as well as data from study C4611007. This starting dose has been selected to balance the safety of trial participants while maintaining the C_{ss} >EC_{90} through the entire dosing interval and is intended not to exceed the initial PK stopping limits, CCI [redacted] (Table 5).

Emerging PK data from those who received active treatment of 500 mg in Part 1 suggest that the exposures (C_{max} and AUC) of the active moiety PF-00835231 were roughly 2-fold (AUC_{24}) to 3-fold (C_{max}) higher compared to those observed in healthy participants (C4611007) based on geometric mean values. The $t_{½}$ was similar to those in healthy participants when values could be calculated.

Because of the anticipated higher exposure in the patient population as compared to healthy participants and the variability in patients observed so far, 250 mg daily for 5 days dosing regimen will enhance the probability of maintaining the C_{ss} > EC_{90} for patients enrolled. Therefore, this starting dosing regimen will balance achieving antiviral activity while remaining within the initial PK stopping limits CCI [redacted]

If the 250 mg daily for 5 days dosing regimen is safe and well tolerated, further dose escalation will be guided by safety as well as PK of the drug. The escalation increment, if explored will be ≤2.5X (eg, from 250 mg to ≤625 mg). Two optional cohorts may be added to explore higher doses or to repeat a dose to expand the cohort. Dose escalation will only proceed after gaining agreement on the dose level from competent regulatory authorities.

Furthermore, dose escalations will be undertaken in a cautious manner such that systemic exposures of PF-00835231 and PF-07304814 at any dose level in Part 2 will not exceed exposure observed from mid-dose of CCI [redacted] (Section 2.2.1.3).

Projected PK exposure parameters and safety margins of PF-00835231 and PF-07304814 relative to exposure limits for **Part 2** based on initial PK stopping limits at the planned dose are listed in Table 5 and Table 6, respectively. Doses presented are projected based on preliminary PK results from study C4611007.

Table 5. Predicted Human Plasma Total Exposure and Safety Margins of PF-00835231 Relative to Exposure Limits at Planned Dose Levels

Dose (mg)	C_{max} (µg/mL)	AUC_{24} (h*µg/mL)	AUC_{inf} (h*µg/mL)	C_{max}[a] safety margin	AUC_{24}[b] safety margin	AUC_{inf}[b] safety margin
[c]250 x 5	0.545	12.7	NA	2.8	2.2	NA
CCI [redacted]						

c. Predicted based on emerging preliminary PK from study C4611007 assuming linear kinetics; C_{max} and AUC_{24} on Day 5 listed. However, limited emerging PK data from those who received active treatment of 500 mg in Part 1 suggest that the exposures (C_{max} and AUC) of the active moiety PF-00835231 were roughly 2-fold (AUC_{24}) to 3-fold (C_{max}) higher compared to those observed in healthy participants (C4611007) based on geometric mean values.

Table 6. Predicted Human Exposure and Safety Margins of PF-07304814 Relative to Exposure Limits at Planned Dose Levels

Dose (mg)	C_{max} (µg/mL)	AUC_{24} (h*µg/mL)	AUC_{inf} (h*µg/mL)	C_{max}[a] safety margin	AUC_{24}[b] safety margin	AUC_{inf}[b] safety margin
[c]250 x 5	0.230	3.72	NA	3.6	4.1	NA
C C I [redacted]						

c. Predicted based on emerging preliminary PK from study C4611007 assuming linear kinetics; C_{max} and AUC_{24} on Day 5 listed.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit.

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. 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 enrolment 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. Male or female participants between the ages of 18 and 79 years, inclusive, at Screening.

   Note: Participants aged 76 to 79 years of age should have BMI <35 kg/m^2.

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

   - Refer to Appendix 4: Contraceptive Guidance for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

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

3. Confirmed presence of SARS-CoV-2 infection as determined by RT- PCR or another method that measures SARS-CoV-2 viral genetic material or by specific SARS-CoV-2 antigen tests in any specimen (eg respiratory fluid sample, saliva, or blood).

   Note: For **Part 2: MAD**, confirmed presence of SARS-CoV-2 viral genetic material in a sample must be ≤72 hours prior to Screening). A positive result from a test that was collected ≥72 hours prior to Screening may be accepted if the site is unable to obtain a repeat sample CCI [redacted]

4. Hospitalized for treatment of COVID-19.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Weight:

6. Total body weight ≥50 kg (110 lb), BMI <40 kg/m^2.

   Note: Participants aged 76 to 79 years, inclusive, should have BMI <35 kg/m^2.

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Evidence of critical illness at the time of Screening and randomization, defined by at least one of the following:

   a. Respiratory failure: Requirement for mechanical ventilation or ECMO, or clinical diagnosis of respiratory failure (ie, clinical need for mechanical ventilation or ECMO, even if not able to be administered in a setting of resource limitation).

   b. Multi-organ dysfunction/failure, as assessed by the investigator.

   c. Cardiac failure or septic shock (SBP <90 mm Hg or diastolic BP <60 mm Hg or requiring vasopressors).

2. Participants that are anticipated by the study Investigator to progress to critical disease, including mechanical ventilation, within 24 hours of enrolment.

3. Participants with pre-existing moderate to severe or poorly controlled cardiovascular disease including hypertension or diabetes, or moderate to severe or poorly controlled chronic lung diseases, including asthma or chronic obstructive pulmonary disease, as assessed by the investigator.

4. Participants with a known medical history of ischemic heart disease, heart failure, dysrhythmia or other pre-existing cardiac condition that in the opinion of the investigator may confuse interpretation of ECG or cardiovascular findings.

5. Participants with a known medical history of recent acute or chronic liver disease (other than non-alcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, or primary biliary cirrhosis.

6. Participants with history of venous thromboembolic event, including deep venous thrombosis or pulmonary embolism.

7. Participants with known HIV infection who have a CD4+ cell count <500/mm^3 and/or who are receiving a boosted anti-retroviral treatment regimen.

8. Participants with a known medical history of recurrent seizures.

9. Confirmed concurrent active systemic infection other than COVID-19.

10. Current diagnosis of cancer, unless in remission and untreated.

11. 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:

12. Participant is receiving any medications or substances that are strong inhibitors or inducers of cytochrome P450 (CYP) 3A4.

13. Participant has received systemic oral, intravenous, or intramuscular corticosteroid therapy (>40 mg/day equivalent prednisolone) within the previous 28 days, except as required for COVID-19 treatment.

14. Female participant who are taking hormonal therapy for contraception or as estrogen replacement therapy, post menopause.

Prior/Concurrent Clinical Study Experience:

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

Note: Participants are allowed to participate if receiving local standard of care for COVID-19 including Remdesivir, convalescent sera/plasma, monoclonal antibody treatments. Participation in an open-label investigational/observational study for convalescent serum/plasma is also allowed so long any associated study procedures do not, in the opinion of the investigator, interfere with the current study. If other therapies receive Emergency Use Authorization status, they may also be allowed after discussion with the sponsor.

Diagnostic Assessments:

16. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious brady-arrhythmias or tachyarrhythmias).

    - If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

17. Participants with any of the following abnormalities in clinical laboratory tests at screening, confirmed by a single repeat test, if deemed necessary:

    - AST or ALT level ≥3 times the ULN.
    - Total bilirubin level ≥1.5 times the ULN, unless due to known Gilbert's syndrome.
    - CL_{cr} <60 mL/min using the Cockcroft-Gault equation.
    - Absolute neutrophil count <1000/mm^3.

Other Exclusions:

18. Females who are pregnant or breastfeeding.

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

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4: Contraceptive Guidance, 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). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once only. All screening assessments must be repeated during re-screening.

5.5. Criteria for Temporarily Delaying Enrolment/Randomization/Study Intervention Administration

Not applicable.

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to PF-07304814 or placebo.

6.1. Study Intervention(s) Administered

6.1.1. Administration

Study intervention administration details will be recorded on the CRF Study Intervention(s) Administered. The IV will be administered on the contralateral arm from PK sampling.

The study interventions are:

Part 1: SAD

- **PF-07304814**: treatment duration = 24-hour continuous intravenous infusion. Study intervention will be provided as a solution for infusion in a vial. Vials are for single use in a single participant for a single dose.

- **Placebo**: treatment duration = 24-hour continuous intravenous infusion.

Part 2: MAD

- **PF-07304814:** treatment duration = 120-hour continuous intravenous infusion. Study intervention will be provided as a powder in vial for solution for infusion. Vials are for single use in a single participant for a single dose.

- **Placebo:** treatment duration = 120-hour continuous intravenous infusion.

Intervention Name	PF-07304814 Solution for Infusion	PF-07304814 Powder for Solution for Infusion	Placebo
ARM Name (group of patients receiving a specific treatment (or no treatment)	PF-07304814	PF-07304814	Placebo
Type	Drug	Drug	Placebo
Dose Formulation	Solution for infusion in a vial. Vial is single-use only	Powder in a vial for solution for infusion. Vial is single-use only	Solution for infusion in a commercial presentation in IV bag
Unit Dose Strength(s)	250 mg as a 25 mg/mL solution	1000 mg	0 mg
Dosage Level(s)	Planned nominal dose over 24h continuous infusion in Part 1: Cohort 1: 500 mg Cohort 2: 1000 mg single dose over 24h.	Planned nominal dose over 120h continuous infusion in Part 2: Cohort 6: 250 mg/day x 5 days Cohort 7: TBD Only used in Part 2.	Part 1: 24h Part 2: 120h
Route of Administration	Intravenous	Intravenous	Intravenous
Use	Experimental	Experimental	Control
IMP or NIMP	IMP	IMP	NIMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided locally by the trial site, subsidiary, or designee.

Intervention Name	PF-07304814 Solution for Infusion	PF-07304814 Powder for Solution for Infusion	Placebo
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. Please see IP manual for additional details.	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. Please see IP manual for additional details for preparation and blinding.	Placebo will be provided by the trial site in commercial IV bags and prepared according to the IP manual. Please see IP manual for additional details.
Current/Former Name(s) or Alias(es)	PF-07304814	PF-07304814	Placebo

6.2. Preparation/Handling/Storage/Accountability

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

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

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

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

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

6. See the IP manual for storage conditions of the study intervention once diluted.

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

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

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

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention in quantities appropriate to the dose cohort, participant randomization and according to the SoA.

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

PF-07304814 and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in a blinded fashion to the participants.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

Study intervention will be administered by continuous infusion starting on Day 1 as summarized in the SoA.

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

Participants in each cohort will be assigned to receive study intervention according to randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party will be responsible for the preparation and dispensing of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense or visual presentation following randomization.

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.

6.3.2. Breaking the Blind

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

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

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic (start and end time) will be recorded in the source documents and recorded in the CRF. 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.

The site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

A record of the number of PF-07304814 vials dispensed to and the volume of PF-07304814 or placebo administered to each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop times and dates, including times for intervention delays and/or dose reductions, will also be recorded in the CRF.

6.5. Concomitant Therapy

Medications taken prior to dosing will be documented as prior medications. Medications taken after the first dose of study intervention has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in study records with indication, daily dose, and start and stop dates of administration. Participants will be queried about concomitant medication (including topical medications and treatments, over-the-counter and prescription medications and treatments, herbals, and vaccinations) at each visit. Any new concomitant medications or dose changes to current concomitant medications should be evaluated for potential new or worsening adverse events.

Study intervention is to be administered on top of SoC for this study. It is recognized that SoC may change during the course of the study, and it is therefore important to meticulously capture all SoC in the CRF.

Prohibited medications are shown in Appendix 8: Prohibited Medications.

Hormonal therapy for purposes of contraception or postmenopausal replacement therapy will not be allowed to be used in participants (see Appendix 4: Contraceptive Guidance).

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07304814; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Planned nominal doses are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data.

6.6.1. Dose Escalation and Stopping Rules

Dosing of any individual participant may be stopped at any time if it is the Investigator's opinion that the risks outweigh any potential benefit, based on the available individual subject safety data. If possible, the Investigator should contact the Sponsor to discuss before discontinuation. For participants in **Part 2** progression of COVID-19 disease should not automatically lead to stopping dosing, but the Investigator should consider the overall risk benefit. Precautionary **sentinel** dosing will be used in each dose-escalating cohort in **Part 1**. A small cohort of 2 participants (1 receiving PF-07304814 and 1 receiving placebo) will be dosed prior to the remainder of the cohort. All available safety and tolerability data from the 2 sentinel participants up to at least Day 3 at 24 hours post completion of dosing will be reviewed by the Investigator(s) (if available), the study team and IRC. The independent IRC will then determine whether it is safe to proceed to dose the remaining participants in the cohort.

During the SAD (**Part 1**) of the study, emerging safety, tolerability, and PK data will be reviewed by the Investigator(s) (if available), the study team and IRC. The independent IRC will then determine whether it is safe to proceed to the next dose level.

The decision to escalate will be based on a minimum of preliminary PK data through 24 hours (Day 2), available safety and tolerability data through Day 6, and all reported SAEs through to Day 9 in at least **6** participants. In addition, the Investigator(s) (if available), the study team and the IRC will review available safety and tolerability data up to Day 3 and all reported SAEs up to Day 6 in the remaining **2** participants, along with cumulative safety and PK data from prior dose levels.

Progression to **Part 2: MAD** will occur if safety, tolerability, and PK data from the prior **Part 1: SAD** 24h infusion cohorts are determined to be supportive and acceptable by a competent regulatory authority.

During the MAD (**Part 2**) of the study, emerging safety, tolerability, and PK data will be reviewed by the Investigator(s) (if available) and the study team. Competent authorities will be consulted before proceeding to the next higher dose cohort. The decision to escalate will be based on a minimum of preliminary PK data through 120h (end of infusion), available safety and tolerability data through Day 7, and all reported SAEs through to Day 10 in at least **6** participants. In addition, the Investigator(s) (if available) and the study team will review available safety and tolerability in the remaining **2** participants, along with cumulative safety and PK data from prior dose levels.

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. If dose escalation is stopped because of any of these criteria, additional cohort(s) may receive the same or lower doses of the investigational product.

The dose escalation will be terminated based on the following criteria:

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities, considered to be drug-related, in the same organ class, and indicating dose-limiting intolerance.

- Severe nonserious AEs, considered as, at least, possibly related to investigational product administration, in 2 participants at a given dose level (but not participants receiving placebo), independent of within or not within the same system organ class, indicating dose-limiting intolerance.

- In the event of an SAE in a participant receiving active treatment, causality must be fully assessed by the investigator and sponsor. If it is deemed to be not drug related, dosing may continue. If it is deemed to be drug related or unknown by either the investigator or sponsor, dosing will be paused and the SAE will be evaluated by the

independent IRC (for Part 1) or competent regulatory authority (for Part 2). If it is determined that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented after communicating with regulatory agencies. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.

- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made by the independent IRC in Part 1 and a competent regulatory authority in Part 2 of the study, following discussions with the study team and the investigator(s) (if available).

- Other findings that, at the discretion of the independent IRC (in Part 1) or a competent regulatory authority (in Part 2), following discussions with the study team and Investigator(s), indicate that dose escalation should be halted.

- **For Part 1:**

  - If, at any dose level, the average exposure reaches or exceeds the PK stopping limits (Section 2.2.1.3):

    - PF-00835231 (active moiety): C_{max}, free of 0.67 µg/mL and $AUC_{24,\ free}$ of 12.4 µg•h/mL, which corresponding to a total C_{max}, of 1.53 µg/mL and AUC_{24}, of 28.2 µg•h/mL.

    - PF-07304814 (prodrug): $C_{max,\ free}$ of 0.30 µg/mL and $AUC_{24,\ free}$ of 5.5 µg•h/mL, which corresponding to a total C_{max}, of 0.838 µg/mL and AUC_{24}, of 15.1 µg•h/mL. If, based on the observed data, the group mean C_{max} or AUC_{24} (based on total plasma concentration) of the next planned dose is projected to exceed the escalation limits, that dose will not be explored.

  - Progression to the next dose will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data.

- **For Part 2**

  - If the 250 mg daily for 5 days dosing regimen is safe and well tolerated, further dose escalation will be guided by safety as well as PK of the drug. The next dose level may be ≤2.5X of the previous dose level in Part 2 (eg, from 250 mg to ≤625 mg). Dose escalation will only proceed after gaining agreement on the dose level from competent authorities. Furthermore, dose escalations will be undertaken in a cautious manner [redacted] (Section 2.2.1.3).

The Regulatory Authorities will be notified of any participant withdrawn from the study for drug-related safety concerns, or safety-related decision to pause or terminate the study.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include (but are not limited to) the following: AEs, Physician decision, withdrawal by participants.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety and other assessments. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

At the discretion of the Investigator, in the event of a significant safety concern such as changes in renal or cardiac function, infusion of the study intervention may be interrupted or terminated.

If anaphylaxis or a serious allergic reaction is noted, the study intervention should be immediately stopped, and the participant should be discontinued. Additionally, other adverse events or confirmed laboratory abnormalities judged by the investigator to be a significant safety concern should also lead to immediate stop to study intervention.

The Sponsor, in consultation with the independent IRC and/or a competent regulatory agency, may also mandate discontinuation based on review of PK or safety data.

If a participant discontinues study intervention, he/she should complete the “Early Termination” visit (SoA).

In addition, intervention will be discontinued for the following changes in ECG.

ECG Changes

A participant who meets either bulleted criteria based on the average of triplicate ECG readings that are deemed to be related to the administration of PF-07304814 will be withdrawn from the study intervention.

- QTcF >500 msec.
- Change from baseline: QTcF >60 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrolment), 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.

7.1.1. Temporary Discontinuation

In **Part 1: SAD**, if infusion is temporary interrupted, it should be resumed as soon as possible and the complete dose should be administered. Temporary discontinuation for longer than 2 hours is not permitted. Participants may temporarily discontinue from **Part 2: MAD** for up to 6 hours over the 120-h infusion period (if possible, each interruption should be no longer than 2 hours) to reduce risk to the participant at the discretion of the investigator. If study intervention administration is restarted the remaining course will be given. Temporary discontinuation for longer than 6 hours is not permitted.

7.1.2. Rechallenge

Not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Physician decision;
- Pregnancy;
- Study terminated by sponsor.

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

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

The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

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

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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

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

The total blood sampling volume for individual participants in this study is approximately 225 mL in **Part 1: SAD** and 360 mL in **Part 2: MAD**. 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 60 consecutive days.

Note: In order to draw blood samples for safety assessments, pharmacokinetics, CCI [redacted] a central line or midline is **not** required by the study protocol, and should only be placed if clinically warranted;

- During dosing of the interventional product, the blood draws for pharmacokinetics should be done using the contralateral arm to the one being used for infusion of the study intervention. (When a simultaneous blood sample is required for safety assessments, CCI [redacted] it is recommended to use the same venipuncture).

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded (height may be reported by participant if necessary) at screening only.

A targeted physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

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

8.2.2. Vital Signs

Temperature (Oral, Tympanic, Axillary or Temporal), pulse rate, respiratory rate, pulse oximetry/SpO_2, and blood pressure will be assessed. It is preferred that body temperature be collected using the same method for the same participant throughout the study.

Blood pressure and pulse rate measurements will be assessed in the supine position preferably with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Vital signs (to be taken before blood collection for laboratory tests) will include 1 pulse rate and 1 blood pressure measurements.

8.2.3. Electrocardiograms

Triplicate standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times (except for single measurement at screening) specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, RR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position and taken before blood collection for laboratory tests.

Once started, triplicate 12-lead ECGs will be completed within 20 minutes of start of the 1st reading; the triplicate ECG measurements collected before dose administration on Day 1 will serve as each participant's baseline QTc value.

If a) a post-dose QTc interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

ECG data may be locally read for dose escalation purpose and then will be submitted to a central laboratory for measurement and final CSR reporting. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (Appendix 7: ECG Findings of Potential Clinical Concern) and should be evaluated further, as clinically warranted.

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 QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7: ECG Findings of Potential Clinical Concern.

8.2.3.1. Continuous Cardiac Monitoring by Telemetry

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the CRF. In addition, a printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.

Telemetry should be collected using a centralized system to monitor and preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the investigator site, or verifiable arrhythmia quantification is required. To establish a baseline, telemetry should be recorded for at least 2 hours on Day -1 or before dosing on Day 1 of each cohort in **Part 1: SAD**. This may be done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the participant is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.

8.2.4. Clinical Safety Laboratory Assessments

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

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

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

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

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

8.2.5. Pregnancy Testing

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

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

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

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator 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 definitively 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 AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

8.3.3. Follow-up of AEs and SAEs

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

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

Further information on follow-up procedures is given in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.

- 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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

- Spontaneous abortion including miscarriage and missed abortion.

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

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

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information 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 is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Not applicable.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration of the study intervention to the wrong participant, or at the wrong time, or at the wrong dose.

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

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of PF-07304814 greater than twice the intended dose within a 24-hour time period (±2 hours) will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07304814 (whichever is longer). Closely monitor the participant for any AEs/SAEs.

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

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

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

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

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of PF-07304814 and PF-00835231

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL plasma, will be collected into appropriately labeled tubes containing K_3EDTA for measurement of plasma concentrations of PF-07304814 and PF-00835231 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. Collection of samples up to and including 12 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples will be used to evaluate the PK of PF-07304814 and PF-00835231. Samples collected for analyses of PF-07304814 and PF-00835231 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, CCI [redacted] or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures. CCI [redacted]

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

As part of understanding the PK of the investigational product, urine samples may be used for evaluation of the bioanalytical method, metabolite identification, and/or assessment of endogenous biomarkers for drug transporters and/or drug metabolizing enzymes. These data will be used for internal exploratory purposes and will not be included in the clinical study report.

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

Drug concentration information that may 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.

CCI [redacted]

8.5.3. Urine for Analysis of PK PF-00835231 CCI [redacted]

CCI [redacted]

[redacted]

As part of understanding the PK of the investigational product, urine samples may be used for evaluation of the bioanalytical method, metabolite identification, and/or assessment of endogenous biomarkers for drug transporters and/or drug metabolizing enzymes. These data will be used for internal exploratory purposes and will not be included in the clinical study report.

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.8.2. Specified Viral Genetics (RNA)

Residual extracted RNA from nasopharyngeal swab and saliva that were collected for viral load assessment from participants per the SoA, may be used for evaluation of potential genetic viral variants (eg, 3CL gene) that are associated with resistance, clinical activity assessed as part of this study, or to explore AEs. Should genetic viral variants be observed, residual samples or biobanked specimens will be used if necessary, for phenotypic analysis for retrospective evaluation. Residuals of all samples may be banked for up to 5 years for future research. Collection, storage and shipping instructions will be in accordance with the laboratory manual.

8.8.3. Viral Load Assessment

Nasopharyngeal swab and saliva samples will be collected from participants per the SoA, and may be analyzed to measure SARS-CoV-2 viral load by RT-PCR and, if feasible, molecular analysis. Residual viral load samples may be utilized for additional PD analysis. Residuals of all samples may be banked for up to 5 years for future research. Collection, storage and shipping instructions will be in accordance with the laboratory manual.

CCI [redacted]

8.8.5. Specified Protein Research

Approximately 10 mL blood will be collected for plasma PD biomarkers and 10 mL blood will be collected for serum PD biomarkers from participants per the SoA. Assessments may include biomarker endpoints outlined below. In addition, transporter analysis may be conducted. These data will be used for internal exploratory purposes and will not be included in the CSR. Collection, storage and shipping instructions will be in accordance with the laboratory manual.

8.8.5.1. Plasma PD Biomarker Assessments

Plasma samples will be used to assess cytokines of inflammatory response (eg, IL-1B, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13 TNF-α, and IFN-γ) and proteomics. Plasma samples will be collected to assess coagulation markers (eg, PT, aPTT, and D-dimer) and fibrinogen at time points described in the SoA.

Residuals of all samples may be banked for up to 5 years for future research. Collection, storage and shipping instructions will be in accordance with the laboratory manual.

8.8.5.2. Serum PD Biomarker Assessments

Serum samples will be used to assess biomarkers of generalized endothelial damage/anemia (eg, ferritin), cardiac dysfunction (eg, CK, proBNPII, and troponin), haptoglobin, and general markers of sepsis/organ damage (eg, LDH, hsCRP, and cystatin-C), and procalcitonin. In addition, host innate responses will be monitored using serological endpoints (anti-SARS CoV-2). Residuals of all samples may be banked for up to 5 years for future research. Collection, storage and shipping instructions will be in accordance with the laboratory manual.

CCI [redacted]

[redacted]

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

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. Estimands and Statistical Hypotheses

There are no estimands or statistical hypotheses for this study.

9.2. Sample Size Determination

No formal sample size calculation was performed.

The sample size for both **Part 1: SAD and Part 2: MAD** of approximately 8 participants per cohort (6 PF-07304814:2 placebo) has been chosen based on the need to minimize first exposure to humans of a new chemical entity and the requirements to provide adequate safety and toleration information at each dose level.

Participants who discontinue for reasons other than drug-related safety events during the trial may be replaced at the discretion of the Sponsor and Investigator.

9.3. Analysis Sets

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

Population	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or his/her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. 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.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.
Safety	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 Concentration Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported for the given part of the study (**Part 1: SAD** or **Part 2: MAD**).
PK Parameter Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest are reported for the given part of the study (**Part 1: SAD** or **Part 2: MAD**).

Population	Description
Biomarker Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the biomarkers of interest are reported for the given part of the study (**Part 1: SAD** or **Part 2: MAD**).

9.4. Statistical Analyses

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

9.4.1. Primary Endpoint: Safety

All safety analyses will be performed on the safety population. No formal analyses are planned for safety data.

AEs, ECGs, BP, pulse rate, pulse oximetry/SpO_2, clinical laboratory data and infusion site reactions will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and may not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4.1.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time.

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 (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

9.4.2. Secondary Endpoint: Pharmacokinetic Analyses

9.4.2.1. Derivation of Pharmacokinetic Parameters

Plasma PK parameters of PF-07304814 and PF-00835231 to be derived (if data permit) from the concentration-time data using standard noncompartmental methods following 24h or 120h infusion are defined in Table 7 and Table 8, respectively. Urine PF-00835231 PK parameters following 24h infusion are defined in Table 9.

Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 7. Plasma PF-07304814 and PF-00835231 PK Parameters Definitions for Part 1: SAD (24-h Continuous Infusion)

Parameter	Definition	Method of Determination
C_{24}	Concentration at 24h (end of infusion in Part 1)	Observed directly from data
C_{24} (dn)	Dose normalized C_{24}	C_{24}/Dose

Actual PK sampling times will be used in derivation of PK parameters.

Table 8. Plasma PF-07304814 and PF-00835231 PK Parameters for Part 2: MAD (120-h Continuous Infusion)

Parameter	Definition	Method of Determination
C_{120}	Concentration at 120h (end of infusion)	Observed directly from data
C_{max}	Maximum observed concentration	Observed directly from data
C_{ss}	Steady state concentration	Average concentration after achieving steady state
$t_{1/2}$*	Terminal half-life.	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve. Only those data points judged to describe the terminal loglinear decline will be used in the regression.

*If data permit.
Actual PK sampling times will be used in derivation of PK parameters.

Table 9. Urine PF-00835231 PK Parameters Definitions for Part 1: SAD (24-h Continuous Infusion)

Parameter	Definition	Method of Determination
Ae	Amount of unchanged drug excreted in urine over 36 hours for QD dosing.	Sum of (urine volume x urine concentration) for each collection following dosing.
Ae%	Percent of dose excreted in urine as unchanged drug over the dosing interval.	100 × Ae/Dose.

Actual PK sampling times will be used in derivation of PK parameters.

9.4.2.2. Statistical Methods for PK Data

No formal inferential statistics will be applied to the PK data. The PK data for PF-07304814 and PF-00835231 will be reported separately.

The plasma PK parameters listed in Table 7 and Table 8 will be summarized descriptively by dose. The plasma concentrations of PF-07304814 and PF-00835231 will be listed and descriptively summarized by nominal PK sampling time and treatment group. Individual participant, as well as mean and median profiles of the plasma concentration-time data will be plotted by dose using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and log scales.

Dose normalized (to 1 mg) C_{24}, (**Part 1: SAD**) of PF-07304814 and PF-00835231 will be plotted against dose (using a logarithmic scale) and will include individual participant values as well as the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

Urine amounts as listed in Table 9 of PF-00835231 will be listed and summarized descriptively, if data permits.

Additional specifications about the tables, listings, and figures will be outlined in the SAP.

9.4.3. Tertiary/Exploratory Endpoints

The analysis of exploratory endpoints will be detailed in the SAP.

CCI [redacted]

[redacted]

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. However, as this is a sponsor-open study, the sponsor will conduct unblinded reviews of the safety and PK data during the course of the study along with the independent IRC (in Part 1 only) for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or

supporting clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team.

An independent IRC will assess whether it is safe to proceed to continued dosing after a small sentinel cohort of 2 participants within each dose-escalating cohort or if it is safe to dose-escalate to the next dose level within Part 1.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an independent IRC for Part 1. The IRC is independent of the study team and includes Pfizer internal members. Emerging data will be reviewed by the Investigator(s) (if available), the study team and the IRC. 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 to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

The IRC will review the data collected for decision to proceed to dosing of the rest of the cohort after the sentinel cohort in each dose-escalating cohort, as well as to proceed to the next dose level in **Part 1: SAD**. The IRC may also be consulted at other times to review safety data and in the event of unexpected safety findings in study C4611007.

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 and 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.

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 guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant 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 will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant 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 must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

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

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

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 7 days from the previous ICD signature date.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

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 his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. 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.

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

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.

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

Monitoring details describing strategy (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, remote, or on-site monitoring), are provided in the monitoring plan.

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

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

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.

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or 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.

10.1.9. Publication Policy

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

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the SToD system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 10. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other

Hemoglobin
Hematocrit
RBC count
MCV
MCH
MCHC
Platelet count
WBC count
Total neutrophils (Abs)
Eosinophils (Abs)
Monocytes (Abs)
Basophils (Abs)
Lymphocytes (Abs)
	BUN
	serum creatinine (and eGFR using Cockcroft-Gault)
	Glucose
	Calcium
	Sodium
	Potassium
	Chloride
	Total CO_2 (bicarbonate)
	AST, ALT
	Phosphorus
	Total bilirubin
	Alkaline phosphatase
	Uric acid
	Albumin
	Total protein
	Lipid panel (Part 2 only)
		pH
		Glucose (qual)
		Protein (qual)
		Blood (qual)
		Ketones
		Nitrites
		Leukocyte esterase
		Urobilinogen
		Urine bilirubin
		Microscopy[a]
			At screening only:
			• FSH[b]
			• Pregnancy test (β-hCG)[c]
			
			At timepoints in SoA:
			• **Coagulation**
			  • D-dimer
			  • PT/INR
			  • aPTT
			• Fibrinogen

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
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 detained (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 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (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, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/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/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/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/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:

- **Mild**: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality**

for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

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

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive 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 3 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

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

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

- Premenopausal female with 1 of the following:
    - Documented hysterectomy.
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.

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

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

- 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.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

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. Female participants utilizing hormonal contraception, including those with hormonal intrauterine devices placed, cannot participate in the study since hormonal contraception is not permitted.

Highly Effective Methods That Have Low User Dependency

1. Non hormonal intrauterine device
2. Bilateral tubal occlusion.
3. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

- **Highly Effective Methods That Have Low User Dependency**

4. 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.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

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 an “adaptor” or are “susceptible.”

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, 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, 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 and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 msec.
 	
• New ST-T changes suggestive of myocardial ischemia.
 	
• New-onset left bundle branch block (QRS >120 msec).
 	
• New-onset right bundle branch block (QRS >120 msec).
 	
• Symptomatic bradycardia.
 	
• Asystole:
 	
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
 	
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
 	
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
 	
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
 	
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

10.8. Appendix 8: Prohibited Medications

Use of any medication or substance that are strong inhibitors (Table 11) or inducers (Table 12) of CYP3A4 is not permitted. Examples of some common medications that are strong inhibitors or inducers CYP3A4 are provided in the tables below. These lists are not comprehensive.

Table 11. Common Medications That Inhibit CYP450 3A4[a]

Category	Examples
Antiretrovirals	Indinavir, nelfinavir, ritonavir, saquinavir, delavirdine, amprenavir, fosamprenavir, atazanavir, cobicistat, lopinavir, danopravir, boceprivir
Antifungal:	Itraconazole, ketoconazole, voriconazole, posaconazole
Anti-infectives	Macrolides: telithromycin, clarithromycin
Antidepressants	Nefazodone
Antineoplastic	Idelalisib

a. Not a comprehensive list.

Table 12. Common Medications That Induce CYP450 3A4[a]

Category	Examples
Anti-infectives	Rifampin
Anti-epileptic	Phenytoin, carbamazepine
Psychoactive drugs	St. John's wort

a. Not a comprehensive list.

For concomitant medications metabolized primarily via CYP3A, recommendations for dose modifications and/or precautions should be implemented according to their labeled drug interaction potential with CYP3A inhibitors.

For concomitant use of drugs that are substrates of P-gp, BCRP, OATP1B1/1B3, OCT1, and MATE1/2K transporters, recommendations for dose modifications and/or precautions should be implemented according to their labeled drug interaction potential with transporters inhibitors.

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
Abs	absolute
ACE	angiotensin converting enzyme
ACE2	angiotensin converting enzyme 2
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ARDS	Acute Respiratory Distress Syndrome
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the curve from time 0 to 24 hours
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration
$AUMC_{inf}$	area under the first moment curve from time 0 extrapolated to infinite time
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BCRP	breast cancer resistance protein
BID	twice daily
BLQ	below limit of quantification
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
C_{24}	concentration at 24 hours
C_{120}	concentration at 120 hours
CC_{50}	50% cytotoxic concentration
C_{eff}	efficacious concentration
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
C_{last}	last quantifiable concentration
CL_p	plasma clearance
C_{min}	minimum observed concentration
C_{max}	maximum observed concentration
$C_{max, free}$	maximum free observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials

Abbreviation	Term
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CPE	cytopathic effect
CL_{cr}	creatinine clearance
COVID	Corona virus infectious disease
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
C_{ss}	concentration at steady state
CT	Clinical trial
CT Scan	computerized tomography scan
CTG	Cell Titer-Glo (luminescent cell viability assay)
CV	cardiovascular
CYP	Cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
dn	Dose normalized
DNA	deoxyribonucleic acid
DOF	duration of IV infusion
DVT	deep vein thrombosis
EC	ethics committee
EC_{50}	50% effective concentration
EC_{90}	90% effective concentration
ECG	electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	electronic case report form
EDP	exposure during pregnancy
EGFP	enhanced green fluorescent protein
eGFR	estimated glomerular filtration rate
EI	efflux inhibitor
EMA	European Medicines Agency
EOT	end of treatment
EU	European Union
EUA	Emergency Use Authorization
EudraCT	European Clinical Trials Database
FDA	Food and drug administration
FIP	First in Patient
fm	fraction of metabolism
FOB	functional observation battery
FSH	follicle-stimulating hormone
FU	follow-up

Abbreviation	Term
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
h	hour(s)
HAE	human airway epithelium
HCV	hepatitis C
hERG	human Ether-a-go-go Related Gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
hsCRP	high sensitivity C-Reactive Protein
Huh7	human hepatocellular carcinoma cells-7
HV	healthy volunteer
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonization
ID	identification
IFN-γ	Interferon gamma
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IP-10	interferon-inducible protein 10
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRC	internal review committee
IRT	Interactive Response Technology
IV	intravenous
K_3EDTA	dipotassium ethylenediaminetetraacetic acid
K_{el}	terminal phase rate constant
LBBB	left bundle branch block
LDH	Lactate dehydrogenase
LFT	liver function test
Log_e	natural logarithm
MA	mouse-adapted
MAD	multiple ascending dose
MATE	multidrug and toxic compound extrusion transporter
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

Abbreviation	Term
MRC-5	Medical Research Council cell strain 5 – human lung fibroblast
msec	millisecond
N/A	not applicable
CCI	[redacted]
NIH	National Institute of Health
NIMP	Non-investigational medicinal product
NOAEL	no-observed-adverse-effect level
NYU	New York University
OCT	organic cation transporter
OATP	organic anion transporting polypeptides
PD	pharmacodynamic(s)
PE	Physical exam
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
proBNP	Pro-B-Type Natriuretic Peptide
PT	prothrombin time
PVC	premature ventricular contraction/complex
QRS	Q wave to the end of the S wave corresponding ventricle depolarization
QTc	corrected QT interval
QTcF	corrected QT using Fridericia's formula
qual	qualitative
RBC	red blood cell
Rega	Rega Institute
RNA	ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SAD	single ascending doses
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS	severe acute respiratory syndrome
SARS-CoV-1	Severe Acute Respiratory Syndrome-Coronavirus-1
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2
SBP	Systolic blood pressure
s.c	subcutaneous
SoA	schedule of activities
SoC	standard of care
SOP	standard operating procedure
SpO_2	oxygen saturation
SRI	Southern Research Institute
SRSD	single reference safety document
SToD	study team on demand
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal half-life

Abbreviation	Term
TBD	to be determined
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TI	Therapeutic Index
TNF-α	Tumor Necrosis Factor-α
ULN	upper limit of normal
US	United States
V_{ss}	Steady-state volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential

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