A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (Trial H6: PF-07304814)

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Appendix H6: PF-07304814 – Version 2.0 (17th August 2021)

The content of this appendix is confidential and should only be viewed by persons covered by the CDA entered between Pfizer and NIAID in relation to the TICO / ACTIV-3 study.

This appendix provides detailed information pertaining to the study of this investigational agent. If not stated otherwise, the text in the master protocol gives the approach that will be taken to study this agent.

H.6.1. Introduction and rationale for studying the agent

PF-07304814 is a phosphate ester prodrug of PF-00835231 (active moiety), a potent and selective inhibitor of the SARS-CoV-2 3CLpro, to be administered as an IV infusion treatment for patients hospitalized with COVID-19. PF-00835231 binds in a covalent, reversible manner to the SARS 3CL protease, resulting in broad-spectrum inhibitory activity across the alpha, beta and gamma coronavirus types [1]. 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 (e.g., HIV protease, HCV protease)[2]. No close human analogs of the coronavirus $3CL^{pro}$ are known, which makes the $3CL^{pro}$ an attractive antiviral drug target [3].

Whereas one antiviral agent (remdesivir) has been demonstrated to have clinical benefit in the target population for this trial and is now part of standard-of-care in the USA (see Appendix I), treatment options for critically ill Covid-19 patients are still limited. Combination of antiviral agents, especially those targeting different steps in the virus life cycle, is a frequently employed therapeutic strategy in treating viral diseases. The combination of PF-07304814 together with remdesivir has shown *in vitro* to have additive, if not synergistic, antiviral effect [4]. RDV and PF00835231 have different metabolic pathways which are not expected to interact. Hence, such combination may contribute to improvement in time to sustained recovery.

Pfizer has evaluated the safety, tolerability, and pharmacokinetics (PK) of intravenously administered PF-07304814 in healthy participants in Phase 1 study C4611007. The safety, tolerability, and PK of PF-07304814 has also been assessed in hospitalized COVID patients in Phase 1b study C4611001.

H6.1.1 *Potential risk and benefits from PF-07304814*

PF-00835231 (the active moiety) has been shown to have SARS-CoV-2 antiviral activity *in vitro* [4], and it is intended to reduce virus titers and thereby reduce disease and risk of mortality in SARS-CoV-2 infected patients. On this basis, the potential benefit to individual study participants who receive the study intervention may include a shorter time to clinical recovery, prevention of ICU admission or invasive mechanical ventilation, and/or a lower

probability of progressing to more severe illness or death. The potential benefit of the study, in general, is that it may provide a new treatment option for hospitalized patients with COVID-19 in the context of the global pandemic public health emergency. However, since this is the first study to assess the efficacy of PF-07304814, the benefit is unknown.

Potential risks associated with PF-07304814 include inflammatory effects, noted by changes in peripheral blood WBCs, coagulation parameters, inflammatory cell infiltrates in various tissues, and thrombo-emboli at the infusion site and/or in different tissues. Thrombosis and increased inflammation were observed following prolonged exposure of PF 07304814 in the 14-day non-human primate (NHP) toxicology study [4]. These have no known mechanistic basis and are believed to be both monitorable and reversible. As this is an investigational agent, there is some risk that is mitigated by 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 may be performed. Clinical attention should be paid to manifestations of inflammation or thrombosis.

Data from two clinical studies (C4611001 and C4611007) are available [4]. In the dose-escalation study in healthy volunteers (study C4611007), where PF-07304814 was administered as a 24-hour infusion, there was no evidence of a pro-inflammatory effect clinically or based on laboratory studies at all dose exposures. All reported AEs were mild in severity and none were reported as treatment related. There were no deaths, SAEs, severe AEs or discontinuations due to AEs during this study [4].

Preliminary data is available from the Phase 1b study (C4611001) [4]. In the Single Ascending Dose (Part 1) of the study, 8 participants have completed 24-hour infusion. Doses were 250 mg (2 participants), 500 mg (2 participants) or placebo (4 participants). In the participants given 250 mg dose, 2 AEs, respiratory failure, considered severe and coagulopathy, considered moderate in severity, were reported by 1 participant. Both AEs started more than 15 days after the end-of-treatment (EOT). In participants given 500 mg dose, 3 AEs were reported by 1 participant. One AE of subclavian vein thrombosis, started approximately 24 hours after EOT, was considered severe and serious (SAE). The other 2 AEs were mild. None of the AEs in the active dose group were considered to be treatment-related. In participants who received placebo, 14 AEs were reported by 4 participants. Of these, 12 AEs were mild and 2 AEs, COVID-19 pneumonia and subclavian vein thrombosis, were considered severe and serious (SAEs). One AE of hematuria, mild in severity was considered treatment-related by the Investigator, blinded to the study treatment assignment. No evidence of sustained proinflammatory effects were noted via laboratory tests which included assessment of hsCRP, coagulation parameters (aPTT, PT, D-dimer), ferritin, and fibrinogen, among others.

In the Multiple Ascending Dose (Part 2) of C4611001, in hospitalized patients with COVID-19, 7 participants received 250 mg and 6 participants received 500 mg of the agent over a 24-hour period for 5 consecutive days. Four participants received placebo for the same

duration. In participants who received 250 mg dose for 5 days, 13 AEs were reported by 4 participants. Of these, 6 AEs were mild, 4 AEs were moderate, and 3 AEs were considered severe and serious (SAEs). Of the 3 SAEs, 2 SAEs of acute respiratory distress syndrome (ARDS) and pneumonia were reported in 1 participant starting on Day 2 of treatment and 2 days post-end of treatment, respectively. One SAE of dyspnoea, reported in 1 participant, started on Day 1 and lasted for 2 days. In participants who received 500 mg dose, 4 AEs were reported in 2 participants. 3 AEs were mild in severity and 1 AE of pulmonary embolism (PE), was considered severe and serious (SAE) and identified on Day 4 of infusion of the treatment. The SAE was considered un-related to the study drug treatment by the Investigator. The participant's D-dimer levels were elevated at entry and it was suspected that the participant had the pulmonary embolism on study entry, but it was undetected at that time. None of the other AEs also were considered to be treatment-related. In participants who received placebo, 9 AEs were reported in 3 participants. Of these, 4 AEs were mild, 3 AEs were moderate and 2 AEs were considered severe and serious (SAEs). One AE of liver function test increased, mild in severity, was considered to be treatment-related by the Investigator, blinded to study drug assignment. The participant was discontinued from the study after 4 days of treatment. The 2 SAEs of hypoxia and PE were reported in 1 participant on Day 5 of treatment and 2 days post-end of treatment, respectively. The participant had a fatal outcome on Day 16 in the study due to AE of hypoxia.

Regarding clinical laboratory assessments, no evidence of sustained proinflammatory effects were noted. Laboratory tests included assessment of hsCRP, coagulation parameters (aPTT, PT, D-dimer), fibrinogen, among others.

Overall, based upon available preliminary data from the Phase I studies, PF-07304814 exhibits an acceptable safety profile. Following the institution of a clinical hold in May 2021 to review the unblinded data from study C4611001, the US FDA concluded in July 2021 that "the current benefit-risk assessment supports continued clinical development of PF-07304814, but only in the context of a PF-07304814 dose cap in clinical studies until more data are available." The current dose cap for PF-07304814 in patients is 250 mg per 24 hours for 120 hours.

More detailed information about the known and expected benefits and risks (including adverse events) of PF-07304814 may be found in the Investigator's Brochure (IB) [4].

Given the safety results of nonclinical studies with PF-07304814 and PF-00835231, the available clinical data with PF-07304814 from Phase 1 studies and the limited disease-directed treatment options for patients with COVID-19, the potential risks identified in association with PF-07304814 are justified by the anticipated benefits that may be afforded to participants hospitalized with COVID-19.

H6.1.2 *Motivation for agent selection by the ACTIV Trial Oversight Committee (TOC)*
The ACTIV Agent Prioritization Committee Antiviral Subteam reviewed the Pfizer PF-07304814 agent, which is an IV continuous infusion antiviral against the SARS-CoV-2 virus and voted in favor of the agent proceeding into ACTIV-3, and the TOC endorsed that recommendation. During the review of Pfizer's PF-07304814, reviewers felt that they would have liked to see more clinical information in the data packet, including information related to combination effects with remdesivir, which could have identified a potential drug-drug interaction (DDI). Despite these limitations, reviewers felt the application was very strong and that the agent's high potency and sufficient lung exposure merit advancement into ACTIV-3 (because continuous infusion is most feasible in an inpatient population). Reviewers noted that this one of the first new and unique antiviral agents developed for SARS-CoV-2 could help evaluate viral replication in various stages of COVID-19 disease which made it important to include in ACTIV-3. Reviewers noted that escape variants should be monitored for changes in this agent's target, but that PF-07304814 should hold up well. Reviewers felt emerging variants were likely given that Gilead is currently investigating cases of remdesivir resistance, and this drug would likely need similar studies. Overall, the Antiviral Subteam members recommended advancing the agent into ACTIV-3 with the contingency that the Antiviral Subteam review additional Phase I and PK data as they become available.

Pfizer's statement regarding plans for licensure:

At the time of study initiation, Pfizer's intent is to make the investigational product available in countries where the trial occurs if the investigational product is proven to be safe/effective. The actual decision to pursue licensure may be impacted by other factors which may include but are not limited to the status of the COVID-19 pandemic in the country and medical need; the impact of COVID-19 on Pfizer's business; decisions by regulatory authorities impacting labeling or marketing, manufacturing processes, safety and/or other matters; supply feasibility issues, including availability of raw materials to manufacture and other matters related to drug supply; availability of other therapies including vaccines; and other regulatory and manufacturing considerations.

H6.1.3 Justification for dose chosen for PF-07304814
The dose of PF-07304814 to be studied in this protocol is 250 mg/day for 5 days, given as a constant rate intravenous infusion. The selected dose is based on clinical pharmacology and safety data, nonclinical pharmacology, in vitro pharmacology, and toxicology findings.

Preliminary data from study C4611001 in hospitalized COVID-19 patients indicate that at the dose of 250 mg/day for 5 days, the preliminary clinical safety profile of PF-07304814 is acceptable. Draft pharmacokinetic data for the active moiety PF-00835231 (based on the first 6 of 8 patients) in the 250-mg / 5 day cohort indicated that the unbound exposures relative to the monkey NOAEL in the 14-day GLP-toxicology study are 1.2x and 1.1x for AUC_{24} and C_{max}, respectively. Additionally, the mean unbound concentration at steady

state was approximately 1.9x the in vitro unbound EC_{90} and all actively treated participants maintained concentrations above the free EC_{90} concentration from 24 hours after the beginning of infusion to the end of infusion.

Based on the above, a dose of 250 mg/day for 5 days, administered as a constant rate intravenous infusion is expected to be safe and associated with therapeutic effect.

H6.2. Agent specific eligibility criteria

In addition to the inclusion and exclusion criteria outlined in the master protocol, the following patients will be excluded:

1. Participants with moderate to severe hepatic impairment (i.e. Child-Pugh class B or C) or acute liver failure.
2. Participants receiving any medications or substances that are strong inhibitors or inducers of cytochrome P450 (CYP) 3A4 (see Section H6.3.4).
3. Patients will be excluded if taking drugs which have a narrow therapeutic window that are substrates of CYP3A4, including but not limited to: astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, pimozide, quinidine, sirolimus, tacrolimus, and terfenadine.
4. Pregnant women
5. Nursing mothers
6. Women of child-bearing potential who are unwilling to acknowledge the strong advice to abstain from sexual intercourse with men or practice appropriate contraception through 5 weeks of the study.
7. Men who are unwilling to acknowledge the strong advice to abstain from sexual intercourse with women of child-bearing potential or to use barrier contraception through 5 weeks of the study.
8. Patients with a history of deep vein thrombosis or pulmonary thrombotic embolism*.

*Prior to the initial futility assessment which is performed when approximately 150 patients have been enrolled on PF-07304814 and 150 on placebo, patients with a history of deep vein thrombosis or pulmonary embolism will be excluded. These patients will be eligible for the trial if the initial futility assessment is passed by this agent, and if risk-benefit is favorable based on an assessment of available data that is reviewed by the independent DSMB. These data will include treatment comparisons of thromboembolic events and coagulation markers, and any additional data from studies carried out by Pfizer.

No other specific inclusion or exclusion criteria need to be altered.

H6.3. Description of investigational agent

H6.3.1. Administration and duration

See the PIM and Pharmacy Procedures for details.

PF-07304814 250 mg daily dose will be administered as a continuous intravenous infusion with a treatment duration of five days or as long as the participant's clinical presentation requires continued hospitalized, should this be shorter than five days. A volume of approximately 250 mL will be infused over each 24-hour period and replaced with a newly prepared infusion bag every 24 hours.

H6.3.2. Formulation and preparation

PF-07304814 1000 mg/vial Powder for solution for infusion is a lyophilized sterile drug product and is packaged in an open label fashion as one single use vial in a carton.

Placebo is 0.9% sodium chloride, also commonly referred to as normal saline.

See Table H6.1 for summary of study medication. The preparation and administration instructions are detailed in the PIM and Pharmacy Procedures. The study medication is prepared by an unblinded pharmacist at the local pharmacy. To ensure blinding of the participant and clinical staff a colored sleeve will be placed over the infusion bags used.

PF-07304814 should be prepared and dispensed as soon as possible after randomization and administered as a continuous infusion through a dedicated IV line. Refer to the PIM and Pharmacy Procedures for the storage conditions of the reconstituted product as well as the timeframe within which the infusion bag is to be fully administered.

Table H6.1. Study medication overview.

Intervention Name	**Control**	**PF-07304814**
Dose Formulation	0.9% sodium chloride solution	PF-07304814 1000 mg/vial Powder for Solution for infusion (diluted in 0.9% sodium chloride solution)
DosageLevel(s) (mg)	Not applicable	250 mg/day
Route of administration	IV infusion	IV infusion
Use	Control	Experimental
IMP and NIMP	NIMP	IMP
Sourcing	Commercially available 0.9% sodium chloride solution in bags	Pfizer
Packaging and Labeling	Commercially available 0.9% sodium chloride solution in bags	Study intervention will be provided in 20mL single-use glass vials individually packaged and labelled appropriately. To be diluted in commercially available 0.9% sodium chloride solution in bags

H6.3.3 Supply, distribution, and accountability

Procedures for ordering and accepting drug, for maintaining inventory of PF-07304814, and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

H6.3.4. Contraindicated medications

Based on human *in vitro* and animal *in vivo* data to date, the major clearance pathway for PF-00835231 is predicted to be via CYP3A4 metabolism (with an estimated 76% metabolized via CYP3A4). Therefore, concomitant use of any medications or substances that are strong inhibitors (Table H6.2) or inducers (Table H6.3) of CYP3A4 are contraindicated. Examples of the most common medications likely to be encountered in patients hospitalized with COVID-19 that are considered strong inhibitors or inducers of CYP3A4 are provided in the tables below. These lists are not necessarily comprehensive.

Table H6.2. Common Medications That are Strong Inhibitors of 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 H6.3. Common Medications That are Strong Inducers of CYP450 3A4[a]

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

a. Not a comprehensive list.

The proposed major clearance mechanism for remdesivir is via carboxylesterase (80%) with minor contributions by cathepsin A and CYP3A4. Remdesivir is also a weak inhibitor of CYP3A4. There is no known significant DDI risk when combining Remdesivir and PF-07304814 (targeting active moiety PF-00835231 plasma concentrations of 0.5 to 1.5 μM), neither as a perpetrator nor as a substrate/victim.

H6.4. Clinical and laboratory evaluations

H6.4.1 Timing of Assessments

Appendix B in the master protocol outlines the timing of clinical and laboratory monitoring. The following assessments will be added to the safety blood tests, analyzed at the local laboratory used by the department for routine diagnosis, and drawn at Day 0 and Day 5:

Prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer, and fibrinogen.

PF-07304814/matching placebo is infused continuously for up to 5 days. Infusion-related AEs will be collected each day for the entire duration of the infusion. Reporting of other safety-related events is outlined in Section 10 of the master protocol.

H6.4.2. Pharmacokinetic and Special Safety Assessments

PK and special safety laboratory assessments will require 1 mL of the plasma and 1 mL of the serum from certain venous blood samples collected as described in the Master Protocol Appendix B as "Research Sample Storage". Aliquots from samples collected on Days 0, 1, 3, and 5 will be used to determine PF-07304814 and PF-00835231 concentrations (as well as potentially other metabolites of PF-07304814) and special safety assessments. Attempts should be made to collect the Day 1 and 3 samples at least 2 hours before or 2 hours after change of the infusion bag. At selected sites, Day 1 and Day 3 plasma samples will be collected using procedure described in the PIM.

PK will be assessed by a validated assay at a bioanalytical lab. Analysis of samples from control subjects is not planned. Results will be forwarded to Pfizer and to the central database for TICO at the University of Minnesota.

Special safety analyses will be conducted in a central laboratory. Samples from control subjects will be analysed for comparison with the active treated group. Results will be forwarded to Pfizer and to the central database for TICO at the University of Minnesota. Remaining samples may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate. Samples may be shipped to the lab for analyses in batches as the trial is unfolding. Results from such analyses will be returned to the trial central database. Treatment comparisons using these data and using other data on the participants will remain blinded to investigators in the trial until the trial is unblinded.

H6.5. Clinical management issues

<u>As part of standard-of-care, it is recommended that participants be placed on medication (heparin being the typical choice) in order to reduce risk of thrombotic events.</u>

Although Fentanyl and Alfentanil have narrow therapeutic windows and are substrates of CYP3A4, it can be used in participants while being infused with PF-07304814, but with caution as plasma levels may increase while co-administered with PF-07304814.

<u>Suspicion of DVT and other thromboembolic events</u>: Withdraw participant from study infusion and proceed with diagnostic and therapeutic interventions per standard of care.

<u>Allergic reactions</u>: Withdraw participant from study infusion and proceed with therapeutic interventions per standard of care.

Blockage of infusion line/pump: Replace venous access as soon as possible. Up to 2 hours interruption of infusion is allowed per 24-hour period of continuous infusion.

Treatment with strong inducers or strong inhibitors of CYP 3A4 may be resumed after discontinuation of study medication.

H6.5.4. Adverse Events of Special Interest (AESI)
Thrombotic events (myocardial infarction, ischemic and hemorrhagic strokes, deep vein thrombosis (including those associated with inserted lines), and pulmonary embolism).

These serious events are reported promptly as PSEEs (see master protocol for details) and are additionally reported as SAEs if considered to be potentially related to the investigational agent.

H6.5.5. Incident Pregnancy in Participants or Their Partners
The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

This study agent will be immediately discontinued if pregnancy is discovered in a participant during the dosing period; however, the participant will not be withdrawn from the study. The participant will continue follow-up in the protocol and should complete all protocol defined visit procedures. The maternal and fetal outcomes, directly relevant to the pregnancy, will be requested, and will be reported on the Pregnancy Outcome eCRF.

If an investigator learns that a male participant's partner has become pregnant after exposure to this study agent, and the male participant is still in this study, the investigator is asked to attempt to obtain relevant information on the pregnancy, and in particular, its outcome, after obtaining consent from the pregnant partner. The outcome of the pregnancy will be reported on the Pregnancy Outcome eCRF.

H6.6. References

1. Hoffman, R.L., et al., *Discovery of Ketone-Based Covalent Inhibitors of Coronavirus 3CL Proteases for the Potential Therapeutic Treatment of COVID-19.* Journal of medicinal chemistry, 2020. **63**(21): p. 12725-12747.
2. Kim, J.C., et al., *Coronavirus protein processing and RNA synthesis is inhibited by the cysteine proteinase inhibitor E64d.* Virology, 1995. **208**(1): p. 1-8.
3. Cannalire, R., et al., *Targeting SARS-CoV-2 Proteases and Polymerase for COVID-19 Treatment: State of the Art and Future Opportunities.* Journal of Medicinal Chemistry, 2020.
4. Pfizer, *Investigator's Brochure PF-07304814, Version 2.0, December 2020*. 2020.
5. *Summary of unblinded safety and pharmacokinetic data from section of trial C4611001 studying PF-07304814 dosed 500 mg by 24 hours over 120 hours*, dated 23rd June 2021.