A PHASE 1, OPEN-LABEL, SINGLE-DOSE STUDY TO INVESTIGATE THE MASS BALANCE, METABOLISM AND EXCRETION OF [^{14}C]-PF-07304814 IN HEALTHY PARTICIPANTS USING A ^{14}C-MICROTRACER APPROACH

Study Intervention Number:	PF-07304814
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Phase:	1

Brief Title: A Phase 1 Study to Investigate the Mass Balance, Metabolism, and Excretion of [^{14}C]-PF-07304814 in Healthy Participants.

Document History

Document	Version Date
Amendment #1	16 August 2021
Original protocol	08 May 2021

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

Protocol Amendment Summary of Changes Table

Amendment [1] (16-August-2021)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Multiple sections	Change [^{14}C] PF-07304814 dose from 600 mg (0.5 µCi) to 500 mg (420 nCi).	FDA feedback to reduce the dose of PF-07304814.
Section 5.2 Exclusion criteria	Total ^{14}C radioactivity measured in plasma exceeding 11 mBq/mL at Screening.	To ensure the background radioactivity in plasma will not interfere in accurately measuring [^{14}C] PF-07304814.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: A Phase 1 Study to Investigate the Mass Balance, Metabolism, and Excretion of [^{14}C]-PF-07304814 in Healthy Participants.

Rationale

This open-label, single-dose study in approximately 5 healthy male and female (of non-childbearing potential only) participants has been designed to characterize mass balance and further the understanding of human pharmacokinetics, metabolism, and excretion of PF-07304814 administered at a dose of 500 mg [^{14}C] PF-07304814 containing approximately 420 nCi [^{14}C] PF-07304814 as a constant-rate, continuous IV infusion over 24 hours. The sample size of approximately 5 was selected to ensure at least 4 fully evaluable participants with completed collections of plasma, urine, and fecal samples. This is a standard sample size used for mass-balance/ADME studies which include assessment of metabolic profiling and is not based on empirical data or hypothesis testing criteria.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To confirm mass balance and characterize the routes of elimination of [^{14}C]-PF-07304814 and drug related materials following 420 nCi/500 mg dose of [^{14}C] PF-07304814	• Amount of [^{14}C] recovered in urine and feces, as a percent of the total dose [^{14}C] administered
• To evaluate the PK of PF-07304814 and PF-00835231 in plasma and characterize the PK of total [^{14}C] in plasma	• Plasma PK parameters, including AUC_{last}, AUC_{inf}, C_{max}, T_{max}, C_{24}, CL, V_{ss}, and $t_{½}$ • Total [^{14}C] in plasma and PK of PF-07304814 and PF-00835231 in plasma
Secondary Objective:	**Secondary:**
• To identify metabolites of PF-07304814 in plasma, urine and feces, if possible	• Identification and determination of relative abundance of the metabolites of PF-07304814 in plasma, urine, and feces
• To evaluate the safety and tolerability of a single, 24-hour constant-rate, continuous infusion of 500 mg PF-07304814 containing 420 nCi [^{14}C]-PF-07304814 in healthy participants	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, physical exam, and 12-lead ECGs

Overall Design

Brief Summary

This is a Phase 1, open-label, single-dose, single-center study to characterize mass balance and evaluate the pharmacokinetics, metabolism, and route and extent of elimination of [^{14}C]-PF-07304814 in healthy male and female (of non-childbearing potential) participants. The study will enroll approximately 5 healthy participants. Each participant will receive a single, 24-hour constant-rate, continuous IV infusion of 500 mg PF-07304814 containing approximately 420 nCi [^{14}C] PF-07304814.

Healthy participants will be screened to determine eligibility within 42 days prior to dosing to confirm that they meet the inclusion and not the exclusion criteria specified in Section 5.1 and Section 5.2, respectively. Medical history and results of physical examination, vital signs, 12-lead ECGs, and clinical laboratory evaluations will determine eligibility. Participants will admitted to the clinical research unit (CRU) on Day -1 and remain in the CRU until the end of the study through Day 10.

On Day 1, each participant will receive a single, 24-hour, constant rate, continuous IV infusion of 500 mg PF-07304814 containing approximately 420 nCi [^{14}C] PF-07304814. Serial blood samples will be collected at specified times (see SoA for details) up to 216 hours post the start of the infusion. Total urine collections will be made just before dosing ("blank") and in 24-hour intervals until the end of the study. Feces will be collected from Day -1 ("blank"), and at the time of passing while the participant is confined in the clinic. Daily sample collections will continue through the morning of discharge. Participants will be confined from at least 24 hours prior to dosing on Day 1 until at least the morning of Day 10 (216 hours) post infusion start.

Complete physical examinations, BP, pulse rate, oral temperature, ECGs, and safety laboratory tests will be conducted, and AEs and concomitant medications will be monitored throughout the study to assess safety. Before the participant is released, a complete physical examination will be conducted along with safety labs, ECG, BP, heart rate and oral temperature.

A safety follow-up call will be made to participants 28 to 35 days from administration of the dose of study intervention.

Number of Participants

Approximately 5 participants will be enrolled to receive study intervention.

Note: "Enrolled" means a participant's, or his legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are

screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Each enrolled participant will receive a single, 24-hour constant-rate continuous IV infusion of 500 mg PF-07304814 containing approximately 420 nCi [^{14}C] PF-07304814.

The total planned duration of participation, from the Screening visit to the last Follow-up phone call, is approximately up to 11 weeks.

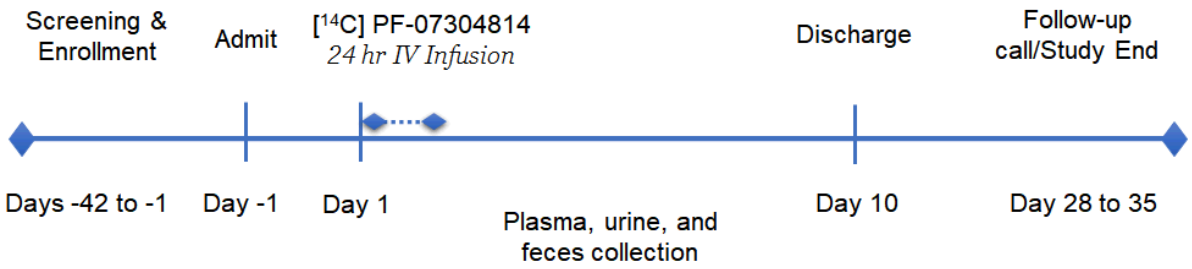
Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

There is no formal research hypothesis to be statistically tested for this study. The purpose of this study is to assess the PK, metabolism, routes and extent of elimination, as well as safety and tolerability of a single, 24-hour constant-rate, continuous IV infusion of 500 mg PF-07304814 containing approximately 420 nCi [^{14}C] PF-07304814 in healthy participants.

1.2. Schema

Figure 1. Study Schema



1.3. Schedule of Activities

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

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

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8.	**Screening**	**Study Period**																	**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Day -42 to Day -2**	**Day -1**	**Day 1**							**Day 2**				**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 10**	**28-35 Days**[t]	
Hours After Start of Infusion			predose	0	0.5	1	2	6	12	24	25	27	32	48	72	96	120	144	216		
Informed consent	X																			
CRU confinement[b]		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		
Inclusion/exclusion criteria	X	X																		
Medical/medication history (update)[c]	X	X																		
Physical exam[d]	X	X																X		X
Safety laboratory[e]	X	X									X			X		X		X		X
Demography[f]	X																			
Contraception check[g]	X	X																	X	
Urine drug testing[h]	X	X																		
FSH (females only)	X																			
12-Lead ECG[i]	X	X	X						X					X				X		X
Blood pressure, pulse rate, and temperature[j]	X	X	X				X		X		X							X		X
HIV, HBsAg, HCVAb	X																			
COVID-19 questionnaire[k]	X	X																		
COVID-19 testing[l]	X	X													X					
COVID-19 check temperature[m]	X	X	X								X			X	X	X	X	X	X	X

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8.	**Screening**	**Study Period**																		**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Day -42 to Day -2**	**Day -1**	**Day 1**							**Day 2**				**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 10**	**28-35 Days**[t]	
Hours After Start of Infusion			predose	0	0.5	1	2	6	12	24	25	27	32	48	72	96	120	144	216		
PF-07304814 administration[n]				X	→	→	→	→	→	X											
Blood sample for PK Total [^{14}C][o]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for unlabeled PF-07304814 & PF-00835231 PK[o]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for metabolite profiling[p]			X		X			X		X				X		X			X		
Fecal collection[q]		X → X		0-24 hour						24-48 hour				48-72 hour	72-96 hour	96-120 hour	120-144, 144-168, 168-192, and 192-216 hour				
Urine collection[r]			X	0-24 hour						24-48 hour				48-72 hour	72-96 hour	96-120 hour	120-144, 144-168, 168-192, and 192-216 hour				
Retained Research Sample for Genetics (Prep D1)[s]		X																			
CRU discharge																			X		
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X

a. Day relative to start of study intervention (Day 1).
b. Participants will be admitted to the clinic on Day -1. Participants will be discharged on Day 10 following the final assessments.
c. Medical history will include a history of prior illegal drug, alcohol, and tobacco use, as well as blood donation within prior 60 days. Medical history will be recorded at Screening and updated on Day -1.
d. A complete physical exam (PE), without genitourinary evaluation will be performed by trained medical personnel at the investigator site at Screening or Day -1 (height and weight must be obtained at Screening to obtain BMI for eligibility criteria) and on Day 10 prior to discharge. A brief PE may be performed at other designated time points at the discretion of the investigator.

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8.	**Screening**	**Study Period**																		**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Day -42 to Day -2**	**Day -1**	**Day 1**							**Day 2**				**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 10**	**28-35 Days**[t]	
Hours After Start of Infusion			predose	0	0.5	1	2	6	12	24	25	27	32	48	72	96	120	144	216		

e. Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed at the indicated time-points. All the safety laboratory samples must be collected following at least a 4 hour fast. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator.
f. Demographics will include participant race, ethnicity, age, and gender during the screening visit.
g. Participants will be counselled regarding contraception requirements on Screening, Day -1, and Follow-up.
h. Urine drug and cotinine (mandatory) and alcohol urine test (at discretion of investigator) will be performed at Screening and on Day -1. These tests may be performed at any other time at the discretion of the investigator.
i. All ECG assessments will be made after at least a 5-minute rest in a supine position and prior to any blood draws or vital sign measurements.
j. Single supine blood pressure and pulse rate will be performed following at least a 5-minute rest in a supine position. BP and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time.
k. Check exposure to positive case, residence or travel in area of high incidence and COVID-19 related signs and symptoms. To be done at screening and at Day -1.
l. The testing for COVID-19 pathogen by RT-PCR will be performed prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after approximately 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19 like symptoms.
m. To be done at least daily during residence. On days in which vitals are being collected, temperature will only need to be taken once and documented.
n. PF-07304814 will be administered as a constant-rate, continuous IV infusion, over 24 hours.
o. One (approximately 4 mL) blood sample for unlabeled PF-07304814 and PF-00835231PK and one (approximately 4 mL) blood sample for PK of total [^{14}C] analysis will be taken at the following timepoints: pre-dose (a single approximately 20 mL sample will be collected), and at 0.5, 1, 2, 6, 12, 24 (to be taken immediately prior to end of infusion), 25, 27, 32, 48, 72, 96, 120, 144, and 216 hours post the start of infusion. One (approximately 4 mL) blood sample will be collected at screening to measure the total radioactivity.
p. One (approximately 10 mL) blood sample will be collected at the times specified in the table for metabolite profiling.
q. Each bowel movement starting from the time of dosing must be collected at the time of passing while the subject is confined in the clinic. Date, and time must be recorded. A fecal sample from Day -1 to Day 1 prior to dosing (feces “blank”), if possible. If an individual subject has not experienced a bowel movement within 36 hours of their previous bowel movements, fluid intake should be increased and administration of a mild laxative (eg, prune juice or a mild stool softener) should be implemented, with the goal to facilitate at least 1 daily bowel movement. The use of the laxative should be recorded.
r. Urine samples will be collected daily through the morning of discharge. Each urine void must be collected. Each participant will empty his/her bladder prior to dosing, and a 10 mL aliquot from this urine (urine “blank”) will be retained. Postdose urine samples will be collected at voiding and labeled for the appropriate 24-hour time period in which each sample has been collected. At the end of each urine collection period, the total weight will be measured and recorded.

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8.	**Screening**	**Study Period**																	**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Day -42 to Day -2**	**Day -1**	**Day 1**							**Day 2**				**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 10**	**28-35 Days**[t]	
Hours After Start of Infusion			predose	0	0.5	1	2	6	12	24	25	27	32	48	72	96	120	144	216		

s. Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

t. A safety follow-up call will be made to participants 28 to 35 days from administration of the dose of study intervention.

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 constant-rate continuous IV infusion for the treatment of patients hospitalized with COVID-19. Additional information for this compound may be found in the investigator's brochure (IB).

2.1. Study Rationale

The purpose of this study is to characterize mass balance and further the understanding of PK, metabolism, and elimination of PF-07304814 and PF-00835231 (active moiety). The knowledge of routes of elimination and metabolites is useful for evaluating the likelihood of effects of renal or hepatic impairment on the disposition of PF-07304814 and PF-00835231 (active moiety). The biotransformation analysis will be used to identify metabolites of PF-07304814, if possible. The knowledge gained in this study may guide study designs to address potential drug-drug interactions (DDI) and special population studies.

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] As of March 2021, at least 123,500,000 cases have been confirmed worldwide, and at least 2,500,000 deaths have occurred.[2]

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[3], patients who are hospitalized with COVID-19 may have significant morbidity and mortality[4,5], 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.[6-10]

Current Treatment Options

As of February 2021, several vaccines have become available in multiple countries to prevent infection with SARS-CoV-2. However, aside from symptomatic and/or supportive treatments there are still few anti-viral drugs that are available to treat COVID-19. A number of different classes of drugs are being evaluated or newly developed to treat hospitalized patients with COVID-19.

While numerous studies investigating various classes of drugs are ongoing and data are rapidly emerging, a limited number of therapeutic agents have demonstrated clinical benefit in large-scale, randomized, controlled clinical trials. Thus, there remains an urgent need for additional safe and more effective therapeutic interventions that improve time to clinical recovery and that prevent the progression of infection to more severe disease and death. As the first protease inhibitor engineered to specifically target the coronavirus 3CL protease,

PF-07304814 has the potential to provide an important new treatment option for patients with COVID-19, when added to SoC therapy, either alone or in combination with other anti-virals that have alternative mechanisms of action.

Rationale for Development of PF-07304814

PF-07304814 is a phosphate ester prodrug of PF-00835231, a new potent and selective inhibitor of the SARS-CoV-2 3CL protease under development for the treatment of patients hospitalized with COVID-19.

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).[11] 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 therapeutic agents. PF-00835231 has demonstrated selectivity for coronavirus 3CLpro, showing little or no activity against a panel of human proteases, as well as HIV and HCV proteases.

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of PF-07304814 can be found in the current Investigator Brochure (IB).

2.2.2. Nonclinical Pharmacokinetics and Metabolism

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 in 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).

Further details may be found in the IB.

2.2.3. Nonclinical Safety

The toxicity profile of PF-07304814 or PF-00835231 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-days. There were no PF-07304814-related clinical observations, changes in body weights, food consumption, clinical pathology parameters, organ weights, or macroscopic and microscopic findings. Most animals, including controls, had signs of low-grade inflammation as suggested by clinical pathology parameters and histopathological findings of infusion site inflammatory cell infiltrates, and thrombi at infusion site or in lungs, which are likely attributable to infusion/catheter-related procedures.[12] There were no PF-07304814-related effects on respiratory function or micronucleus assessment.

The infusion studies were associated with increased inflammation also noted in the concurrent control groups in both rat and monkey studies. However, exacerbation of infusion/procedure-related inflammatory effects by PF-07304814 was observed in the 14-day GLP monkey study and the highest dose tested (1000 mg/kg/day) was considered above MTD. These effects included changes in peripheral blood WBC counts, coagulation parameters, inflammatory cell infiltrates in various tissues, and thrombo-emboli at the infusion site and/or in different tissues. These effects are monitorable through peripheral blood chemistry, coagulation, and hematology evaluations. Findings in the recovery phase were consistent with resolution of dosing phase inflammation related to the infusion procedure. The NOAEL in the 14-day GLP rat study was 1000 mg/kg/day, representing 16× and 14× the predicted human unbound C_{max} and AUC_{24}, respectively, for the active moiety PF-00835231 at the projected minimum human efficacious dose of 0.5 grams over 24 hours of PF-07304814. The exposures at the highest tolerated dose (360 mg/kg/day) in the 14-day GLP monkey study were 16× and 13× the predicted human unbound C_{max} and AUC_{24}, respectively, for the active moiety PF-00835231 at the projected minimum human efficacious dose. While no direct target organs of toxicity were identified, the NOAEL was identified as 70 mg/kg/day based on severity of procedure-related exacerbation of inflammation. Moderate mixed cell inflammation within the heart and lung observed in a single female at 360 mg/kg/day with evidence of tissue injury was considered adverse. This female had the highest exposure to the active moiety PF-00835231 on Day 14 compared with others in the group. The NOAEL dose of 70 mg/kg/day represent 2.8× and 2.2× the predicted human unbound C_{max} and AUC_{24}, respectively, for the active moiety PF-00835231.

A battery of safety pharmacology endpoints (neurological, respiratory, and cardiovascular) incorporated into the 24-hour or 14-day toxicity studies indicated the lack of safety pharmacology concerns related to the administration of PF-07304814. PF-07304814, and PF-00835231 were negative in the in vitro bacterial reverse mutation assay and did not induce micronuclei formation in vitro or in vivo. Both compounds had minimal potential for secondary (off-target) pharmacology at clinically relevant exposures and were compatible with human blood.

The nonclinical safety profile of PF-07304814 has been adequately characterized to support progression into clinical studies.

Further details may be found in the IB.

2.2.4. Clinical Overview

PF-07304814 has been evaluated in a Phase 1 study (C4611007) evaluating the safety, tolerability and PK of PF-07304814 as a 24-hour infusion in healthy participants (LPLV: 17 December 2020). Preliminary data are also available from a Phase 1b study (C4611001) in COVID-19 patients evaluating the safety, tolerability and pharmacokinetics (PK) of escalating doses of PF-07304814 given as a 24-hour intravenous (IV) infusion in Part 1 and as a 120-hour infusion in Part 2.

Further details may be found in the IB.

2.2.4.1. Summary of Clinical Safety

Study C4611007 consisted of 2 interleaving cohorts with a total of 15 healthy adult participants evaluable for safety data. Single doses of PF-07304814 ranging from 50 to 700 mg were evaluated. At the 50 mg and 500 mg dose level 6 participants were exposed to study drug, at the 150 mg and 700 mg dose level 5 participants were exposed to study drug; 2 participants were exposed to placebo at each dose level.

Following a single 50, 150, 500, or 700 mg dose of PF-07304814 administered as a 24-hour infusion in healthy participants, a total of 20 all-causality treatment emergent adverse events (TEAEs) were reported by 12 participants across the different treatment groups. There were no deaths, serious adverse events (SAEs), severe AEs or discontinuations due to AEs during this study. There were no individual laboratory abnormalities assessed as clinically significant by the Investigator.

In the ongoing study in hospitalized COVID-19 patients (C4611001), as of the data cut-off snapshot (26 March 2021), 8 participants have been enrolled in Part 1 and 8 participants in Part 2. In Part 1, 4 participants were dosed at 250 mg dose (PF-07304814 or placebo) and 4 participants were dosed at 500 mg dose (PF-07304814 or placebo) in a blinded manner. In Part 2, 6 participants were dosed with PF-07304814 at 250 mg/day for 5 days (~120-hour infusion) and 2 participants received placebo for the same duration, in a blinded manner.

Seven TEAEs were reported by 3 participants in Part 1 (24 hour infusion), 250 mg does cohort. Four AEs were considered mild; 1 AE of coagulopathy was considered moderate, and 2 AEs respiratory failure and worsening of COVID pneumonia, were severe. AE of worsening of COVID pneumonia was considered serious (SAE). Except for 1 AE of hematuria experienced by 1 participant, all other AEs were not related to study treatment. In Part 1 (24-hour infusion), 500 mg dose cohort, 12 TEAEs were reported by 3 participants. Ten AEs were mild and 2 were severe and serious (SAEs). None of the AEs were considered treatment-related. Two SAEs of deep venous thrombosis (DVT) of the subclavian vein at the site of the midline placement occurred in 2 participants, 1 of whom was dosed with 500 mg PF-07304814 and the other participant received placebo (sentinel group within the cohort).

In Part 2 (120-hour infusion) 250 mg/day cohort of the ongoing study C4611001, complete data were available from first 6 participants enrolled in the cohort. Of these 6 participants, a total of 2 TEAEs were reported by 1 participant. Both of the AEs were considered to be unrelated to study treatment. Additional, preliminary SAE data were available after the snapshot date (26 March 2021) from last 2 participants enrolled in the cohort. Overall, 3 SAEs were reported by these 2 participants. One participant reported acute respiratory distress syndrome and experienced ventilator-associated pneumonia and the other participant experienced worsening of dyspnea. None of these SAEs were considered related to study treatment.

The preliminary and cumulative data from studies C4611007 and C4611001 show a safety profile that supports continued investigation of PF-07304814 in clinical studies. More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07304814 can be found in the IB.

2.2.4.2. Summary of Clinical Pharmacology

Following single ascending 24-hour IV infusions of PF-07304814 to healthy participants at doses of 50 mg, 150 mg, 500 mg, and 700 mg, near maximum plasma concentrations for PF-00835231 (the active moiety) were generally first observed ~6h post start of the infusion and sustained until the end of the infusion. PF-00835231 plasma concentrations declined rapidly after the end of the infusion with mean t½ values of 1.97 hours and 1.74 hours for the 500 mg and 700 mg doses, respectively where these could be calculated and reported. PF-00835231 systemic exposure based on geometric mean AUC_{last} and C_{max} values appeared to increase in a dose proportional manner across all doses. Geometric mean C_{ss} values also increased in a dose proportional manner across all doses. Based on the geometric mean Ae%, approximately 9%-11% of the PF-07304814 dose was recovered in urine as the active moiety PF-00835231 across all doses.

Following single ascending 24-hour IV infusions of PF-07304814 (a phosphate prodrug) at doses of 50 mg, 150 mg, 500 mg, and 700 mg, geometric mean C_{max} were observed between a median T_{max} of 3 to 16 hours post start of the infusion. Near maximum plasma concentrations of the phosphate prodrug PF-07304814 were generally first observed ~3 hours and sustained until at least 16 hours post start of the infusion. Despite a continuous 24-hour infusion of PF-07304814, plasma concentrations declined before the end of the infusion. t½ values could not be determined since all plasma samples collected after the 16 hours post start of the infusion were below the limit of detection. PF-07304814 systemic exposure based on geometric mean AUC_{last} values appeared to increase in a dose proportional manner between the 150 mg and 700 mg doses, however this relationship could not be fully assessed for the 50 mg dose due to the high variability and levels being close to or near the lower limit of detection (40 ng/mL). Geometric mean C_{max} values and C_{ss} appeared to increase in a dose proportional manner across the dose range studied.

Further details may be found in the IB.

2.3. Benefit/Risk Assessment

PF-07304814 will not provide any clinical benefit to healthy participants. This study is designed primarily to further the understanding of human PK, metabolism, and elimination of PF-07304814 and PF-00835231 (active moiety).

Since the administered radioactivity is very low (eg, <1000 nCi), participants will be exposed to extremely low amounts of radiation and therefore supporting data such as a dosimetry study in animals are not required.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-07304814 may be found in the investigator's brochure, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07304814		
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.	The potential risks are based on the nonclinical study findings. Thrombosis and increased inflammation were observed following prolonged exposure of PF-07304814 noted in the 14-day NHP toxicology study. Information is available in the SRSD for PF-07304814.	As this is an investigational agent, there is some risk that is mitigated by close observation of AEs, vital signs, ECGs and laboratory assessments. Participants with a history of thrombotic events will be excluded.
Study Procedures		
Potential for irritation at the intravenous catheterization site which is required 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 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.
Potential for increased risk of intravenous infusion site reaction.	There may be potential risk for infusion site reaction due to the low pH of study intervention and/or the need for continuous intravenous infusion. These risks are described in the SRSD for PF-07304814.	Monitoring of reactions will be performed through targeted PE and collection of AEs, which will be reviewed on an ongoing basis. If an individual participant is unable to tolerate the continuous infusion, based on AEs, treatment may need to be discontinued.
Other (Not Applicable)		

2.3.2. Benefit Assessment

PF-07304814 will not provide any clinical benefit to healthy participants. The purpose of the study is to characterize mass balance and further the understanding of human metabolism of [^{14}C] PF-07304814.

2.3.3. Overall Benefit/Risk Conclusion

PF-07304814 will not provide any clinical benefit to healthy participants in this study. Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with administration of PF-07304814 are justified by the anticipated benefit, in terms of contribution to the process of developing new therapy in an area of unmet medical need.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To confirm mass balance and characterize the routes of elimination of [^{14}C]-PF-07304814 and drug related materials following 420 nCi/500 mg dose of [^{14}C] PF-07304814	• Amount of [^{14}C] recovered in urine and feces, as a percent of the total [^{14}C] dose administered
• To evaluate the PK of PF-07304814 and PF-00835231in plasma and characterize the PK of total [^{14}C] in plasma	• Plasma PK parameters, including AUC_{last}, AUC_{inf}, C_{max}, T_{max}, C_{24}, CL, V_{ss},and $t_{½}$ • Total [^{14}C] in plasma and PK of PF-07304814 and PF-00835231 in plasma
Secondary Objective:	**Secondary:**
• To identify metabolites of PF-07304814 in plasma, urine and feces, if possible	• Identification and determination of relative abundance of the metabolites of PF-07304814 in plasma, urine, and feces
• To evaluate the safety and tolerability of a single, 24-hour constant-rate, continuous infusion of 500 mg PF-07304814 containing 420 nCi [14C]-PF-07304814 in healthy participants	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, physical exam, and 12-lead ECGs.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, single-dose, single-center study to characterize mass balance and further the understanding of human PK, metabolism, and excretion of [^{14}C] PF-07304814. The study will be conducted in approximately 5 healthy participants. Each participant will receive a single, 24-hour constant-rate, continuous IV infusion of 500 mg PF-07304814 containing approximately 420 nCi [^{14}C] PF-07304814.

Approximately 5 participants will be enrolled. Each participant will be screened to determine eligibility within 42 days prior to dosing to confirm that they meet the inclusion and not the exclusion criteria specified in Section 5.1 and Section 5.2, respectively. Medical history and results of physical examination, physical measurements, vital signs, 12-lead ECGs, and clinical laboratory evaluations will determine eligibility. Participants will be admitted to the CRU on Day -1 and remain in the CRU through Day 10. Participants will be discharged on Day 10 following the final assessments. Participants who withdraw will not be replaced unless the number of completed participants falls below 4. Refer to Figure 1 for details.

On Day 1, each participant will receive a single, 24-hour constant-rate, continuous IV infusion of 500 mg PF-07304814 containing approximately 420 nCi [^{14}C] PF-07304814. Serial blood samples will be collected at specified times (see SoA for details) up to 216 hours post the start of the infusion. Total urine collections will be made just before dosing ("blank") and at 24-hour intervals until the end of the study. Feces will be collected from Day -1 ("blank"), and at the time of passing while the participant is confined in the clinic. Daily sample collections will continue through the morning of discharge. Participants will be confined from at least 24 hours prior to dosing on Day 1 until at least the morning of Day 10 (216 hours) post infusion start.

Complete physical examinations, BP, pulse rate, oral temperature, ECGs, and safety laboratory tests will be conducted, and AEs and concomitant medications will be monitored throughout the study to assess safety. Before the participant is released, a complete physical examination will be conducted along with safety labs, ECG, BP, heart rate and oral temperature.

A safety follow-up call will be made to participants approximately 28 to 35 days from administration of the dose of study intervention.

The total planned duration of participation, from the Screening visit to the last Follow-up phone call, is approximately up to 11 weeks.

4.2. Scientific Rationale for Study Design

This study is a Phase 1 open-label, single-dose study in healthy males and females of non-childbearing potential, designed to characterize mass balance and investigate the PK, metabolism, and excretion of [^{14}C] PF-07304814, characterize plasma, fecal, and urinary [^{14}C] and identify any metabolites, if possible. The knowledge of the metabolism and routes of elimination of PF-07304814, PF-00835231 (active moiety), and associated metabolites is useful for evaluating the likelihood of effects of renal or hepatic impairment on the overall disposition.

The sample size of approximately 5 was selected to ensure at least 4 fully evaluable participants with completed collections of plasma, urine, and fecal samples.

Knowledge gained in this study will help guide study designs to address potential drug interactions and special population studies.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for PF-07304814, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Section 10.4).

4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

The total drug dose of 500 mg PF-07304814 selected for this study is within the anticipated clinically relevant dose range. This dose is below the highest dose evaluated in healthy participants (700 mg IV administered over 24 hours), which was safe and well tolerated. A dose of 500 mg PF-07304814 is expected to result in exposures below those observed following a single, 24-hour constant-rate, continuous IV infusion in healthy participants.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last visit or the last scheduled procedure shown in the SoA.

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 enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female participants must be 18 to 55 years of age, inclusive, at the time of signing the ICD.

    - Women must be of non-childbearing potential: must meet the criteria for WNOCBP outlined in Section 10.4.3.

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

Type of Participant and Disease Characteristics:

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and ECGs.

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

Weight:

4. BMI of 18 to 32 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Positive test result for SARS-CoV-2 infection at the time of Screening or Day -1.

3. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

4. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg, Contact with positive case, residence, or travel to an area with high incidence) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

5. History of thrombotic events.

Prior/Concomitant Therapy:

6. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.8 Concomitant Therapy for additional details).

7. Systemic therapy with any medications that are strong CYP3A4 inhibitors within 28 days or 5 half-lives (whichever is longer) or strong CYP3A inducers within 28 days or 5 half-lives (whichever is longer) prior to dosing of study intervention

8. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.8 Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

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

10. Participants who have received a COVID-19 vaccine within the past 2 weeks; and/or participants who are scheduled to receive a second COVID-19 vaccination dose during the in-clinical period of this study.

Diagnostic Assessments:

11. A positive urine drug test.

12. Screening supine BP >140 mm Hg (systolic) or >90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is >140 mm Hg (systolic) or >90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

13. Standard 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 bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. 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 a participant.

14. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - AST **or** ALT level ≥ 1.0 × ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is≤ ULN;
    - Estimated glomerular filtration rate (eGFR) <70 mL/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration formula.

Other Exclusions:

15. Total ^{14}C radioactivity measured in plasma exceeding 11 mBq/mL at "Screening" .

16. Females who are breastfeeding.

17. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).

18. History of tobacco or nicotine use within 3 months prior to dosing, or a positive cotinine at screening or Day -1.

19. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

20. History of sensitivity to heparin or heparin-induced thrombocytopenia.

21. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

22. Participants with a history of irregular bowel movements eg, less than 1 bowel movement per day, regular episodes of diarrhea or constipation, irritable bowel syndrome (IBS) or lactose intolerance.

23. Participants enrolled in a previous radionucleotide study or who have received radiotherapy within 12 months prior to screening or such that total radioactivity would exceed acceptable dosimetry (ie, occupational exposure of 5 rem per year).

24. Participants whose occupation requires exposure to radiation or monitoring of radiation exposure.

25. 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.

26. Previous exposure to PF-07304814.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample.

- Water may be consumed without restriction. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after the start of infusion.
- Dinner will be provided approximately 9 to 10 hours after the start of infusion.
- An evening snack may be permitted.
- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges or pomelos) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.
- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.
- To help assure regularity in bowel movements, nutritional composition should contain at least 15 g of fiber per 1000 kcal or fiber capsules containing the equivalent amount of fiber may be administered daily (beginning at least 8 hours after dosing).
- If an individual participant has not experienced a bowel movement within 36 hours of their previous bowl movement, fluid intake should be increased and administration of a mild laxative (eg, prune juice or a mild stool softener) should be implemented, with the goal to facilitate at least 1 daily bowel movement. The use of laxative should be recorded.
- Participants will be asked to abstain from indigestible materials, eg, corn, nuts, etc, for 2 days prior to dosing and for the duration of the study in order to facilitate fecal homogenization.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample is collected.
- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample. Participants may undergo an alcohol breath test or urine alcohol test at the discretion of the investigator.
- Participants will abstain from the use of tobacco- or nicotine-containing products for 3 months prior to dosing and during confinement in the CRU.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted;

5.3.4. 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) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may have changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

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

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to PF-07304814, administered as a single, 24-hour constant-rate, continuous IV infusion of 500 mg containing approximately 420 nCi [^{14}C] PF-07304814.

6.1. Study Intervention(s) Administered

[^{14}C]PF-07304814 will be provided by Pfizer as bulk API and, where necessary, bulk excipients for the manufacture of the [^{14}C] labeled IV formulation. The final product composition, sourcing of components and/or excipients, and presentation will be detailed in a separate Technical Agreement (TA) for IV drug product.

6.1.1. Administration

Participants will receive 500 mg PF-07304814 containing approximately 420 nCi [^{14}C] PF-07304814 starting at approximately 08:00 hour (plus or minus 2 hours), administered as a single, 24-hour constant-rate, continuous IV infusion. Administration of [^{14}C] PF-07304814 will be performed by qualified investigator site personnel (in accordance with local regulations and laws). Investigator site personnel will administer study intervention according to the site administration instructions (SAI).

6.2. Preparation, Handling, Storage, and Accountability

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

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

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 a separate TA.

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. 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.

7. Further guidance and information for the final disposition of unused study interventions are provided in the TA. 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.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

[^{14}C]PF-07304814 solution for the IV administration will be manufactured at the clinical study site by 2 trained personnel and quality assurance (QA) released prior to administration. Details of the dose preparation will be provided in a separate TA. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements. Leftover containers following IV administration, including tubing used for infusion, should be shipped to laboratory for assessment of radioactivity, if needed.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

The site staff will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded 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 a preparation record, which may be detailed in the TA. 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.

6.5. Dose Modification

Not applicable.

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

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

6.7. Treatment of Overdose

For this study, any dose of PF-07304814 greater than 700 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07304814 (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

6.8. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day. If an individual participant has not experienced a bowel movement within 36 hours of their previous bowel movements, administration of a mild laxative (eg, prune juice or a mild stool softener) may be used, with the goal to facilitate at least 1 daily bowel movement.

Use of strong CYP3A inhibitors and/or inducers within 28 days or 5 half-lives (whichever is longer) prior to the first dose of investigational product or during the study are prohibited.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

6.8.1. 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.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

7.1.1. ECG Changes

A participant who meets either bulleted criterion on a single ECG will have 2 additional ECGs measured and the average of the triplicate ECG readings recorded. If the average of triplicate ECG readings meets either of the bulleted criterion, the participant will be withdrawn from the study intervention after consultation with the investigator and sponsor.

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

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

Participants will be screened within 42 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 42 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research sample, may be used without repeat collection, as appropriate.

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.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter. Blood samples for PK must not be taken from the same arm used for IV drug administration on the day of drug infusion.

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

The total blood sampling volume for individual participants in this study is approximately 280 mL rounded up to nearest 5 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 500 mL during any period of 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

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, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.2. Vital Signs

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mmHg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. BP should not be taken from the arm with an intravenous infusion (even if that is the dominant arm). Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.2.1. Temperature

Temperature will be measured orally. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTcF intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by >60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is >500 msec for any scheduled ECG. If either of these conditions

occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart and the average of the 3 taken to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then the participant will be withdrawn.

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

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

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

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, 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 5 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. COVID-19 specific assessments

Participants will be tested for SARS-COVID-19 infection by RT-PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after approximately 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the principal investigator.

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

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

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

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

During the active collection period as described in Section 8.3.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

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

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-Up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, 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 calendar 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 preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

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

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

8.3.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Pharmacokinetics, [^{14}C] Assessment, and Metabolite Profiling

Details regarding the processing, storage, and shipping of PK and [^{14}C] assessment samples will be provided in the lab manual.

Blood samples for measurement of plasma concentrations of PF-07304814 and PF-00835231, plasma total [^{14}C], and metabolic profiling will be collected as specified in the SoA. Urine and feces will be collected at the time windows specified in the SoA for total [^{14}C] excretion, and mass-balance. All samples must be processed and shipped as indicated in the instructions provided in order to maintain sample integrity. Any deviations from the sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken must be documented and reported. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. The actual date and time (24-hour clock time) of each sample will be recorded.

Details for measurements are provided in Sections 8.4.1, 8.4.2, 8.4.3for plasma, urine, and feces, respectively. Complete details will be provided in the study manual.

Any remaining plasma, urine, or feces samples may be retained and utilized to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, CCI CCI

8.4.1. Plasma for Analysis

Blood samples will be collected for measurement of plasma concentrations of PF-07304814, PF-00835231, PF-07319509, and PF-03626560 (4 mL/sample, split plasma sample to two aliquots), and total [^{14}C] (4mL/sample), as specified in the SoA. A single 20 mL blood sample will be collected just prior to dosing. Additional blood samples of approximately 10 mL will be collected for plasma metabolic profiling at times specified in the SoA.

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 10 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 collected for analyses of PF-07304814, PF-00835231, PF-07319509, and PF-03626560 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, CCI

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.

Details regarding the collection, processing, storage and shipping of samples will be provided in the lab manual.

Samples collected for measurement of plasma concentrations of PF-07304814, PF-00835231, PF-07319509, and PF-03626560- will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples collected for plasma [^{14}C] determination will be analyzed using AMS. Potential metabolites may be analyzed with CCI validated CCI CCI methods.

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

8.4.2. Urine for Analysis

Urine will be collected for analysis of PF-07304814 and PF-00835231, total [^{14}C] measurement, and metabolite identification within intervals specified in the SoA.

Each participant will empty his bladder just prior to dosing. A 10 mL aliquot from this urine (urine "blank") will be labeled and frozen at –20°C or lower.

Urine samples will be collected post the start of infusion at voiding and labeled for the appropriate 24-hour time period in which each sample has been collected. During the entire collection period, the urine container should be refrigerated. At the end of each urine collection period, the total weight will be measured and recorded. The urine within each collection interval will be mixed thoroughly and aliquoted to assess:

- Fraction of [^{14}C] dose excreted in urine;
- PF-07304814 and PF-00835231;
- Metabolic profiling.

Following completion of analyses and subsample collections for metabolite profiling, the remaining urine samples will be discarded upon approval from the sponsor.

Details regarding the collection volume, processing, storage and shipping of the urine samples will be provided in the lab manual.

8.4.3. Feces Analysis

Feces will be collected for determination of total [14C] measurement and metabolite identification. Fecal voids will be collected within intervals specified in the SoA. Each participant will be required to provide a fecal sample prior to dosing during the time period of Day -1 to Day 1 predose. This entire fecal sample will be labeled as feces "blank" and will be frozen at –20°C or lower. Date, and time must be recorded.

Postdose fecal voids will be collected from each bowel movement into ziploc bags, labeled for the appropriate 24-hour time period in which each sample has been collected, and immediately frozen at –20°C or lower. Once received at the lab, fecal samples will be pulled for the appropriate 24-hour interval and total fecal mass recorded for each 24-hour period. Samples will then be homogenized and 2 fecal homogenate aliquots will be collected to assess:

- Fraction of [^{14}C] dose excreted in feces;
- Metabolic profiling.

In the event of diarrhea during the study, all diarrhea, including any swabbing and contaminated linen, should be collected, labeled, and stored in appropriate containers at -20°C or lower for possible analysis of [^{14}C]. Following completion of analysis and subsample collections for metabolite profiling, the remaining bulk fecal homogenate will be discarded upon approval from the sponsor.

Details regarding the collection, processing, storage and shipping of the feces samples will be provided in the lab manual.

8.5. Genetics

8.5.1. Specified Genetics

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

8.5.2. Retained Research Samples for Genetics

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

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

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

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.6.1. Specified Gene Expression (RNA) Research

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

8.6.2. Specified Protein Research

Specified protein research is not included in this study.

8.6.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.6.4. Retained Research Samples for Biomarkers

Retained research samples for biomarkers will be not be collected in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

Health economics/medical resource utilization and health economics parameters 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 a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

There is no formal research hypothesis to be statistically tested for this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.
Full Analysis Set (FAS)	Example: All participants assigned to study intervention and who take study intervention.
Safety Analysis Set	All participants assigned to study intervention and who take at least 1 dose of study intervention.
PK Concentration Analysis Set	The PK concentration analysis set for PF-07304814 is defined as all participants who receive study intervention and have at least one measurable PF-07304814 and PF-00835231 concentration. The PK concentration analysis set for [^{14}C] is defined as all participants who receive study intervention and have at least one [^{14}C] measurement.

Participant Analysis Set	Description
Mass Balance Analysis Set	All participants who receive study intervention and who have evaluable total [^{14}C] concentration (urinary and fecal) data and who had no protocol deviations or AEs (such as diarrhea or severe constipation) that may have affected the mass balance analysis.

9.3. Statistical Analyses

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

9.3.1. Pharmacokinetic Analysis

9.3.1.1. Mass Balance

Carbon-14 in urine will be measured using accelerator mass spectrometry and reported as the percentage of the administered dose of [^{14}C] excreted at each time interval and as the total percent of dose excreted in urine.

Carbon-14 in feces will be measured using accelerator mass spectrometry and reported as the percentage of the administered dose of [^{14}C] excreted at each time interval and as the total percent of dose excreted in feces.

Percent recovery of total [^{14}C] in urine and feces will be determined based on total administered dose.

Individual participant and median data profiles will be graphically presented for the cumulative recovery of [^{14}C] in urine, feces and their combination. The total recovery of [^{14}C] in urine, feces and their combination will be listed and summarized. Where possible the rate of excretion of [^{14}C] will be estimated.

9.3.1.2. Derivation of Pharmacokinetic Parameters (Plasma)

Plasma PF-07304814 and PF-00835231 (active moiety) concentrations will be reported in units of mass per volume, while total [^{14}C] in plasma will be reported in units of unchanged drug concentration equivalents per volume (eg, ngEq/mL). PK parameters (Table 1) will be derived from PF-07304814 and PF-00835231 concentrations in plasma and from total [^{14}C] concentration equivalents in plasma. Actual PK sampling times will be used for the derivation of PK parameters.

The PF-07304814 and PF-00835231 concentrations and PK parameters and the total [^{14}C] concentration equivalents and PK parameters will be listed and summarized using descriptive statistics. Individual and median PF-07304814 and PF-00835231 concentration-time profiles and total [^{14}C] concentration equivalents-time profiles will be graphically presented.

Table 1. Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
C_{24}	Obsereved plasma concentration at 24 hours	Observed directly from data
$t½^{a}$	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
AUC_{last} [a]	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/log trapezoidal method
AUC_{inf} [a]	Area under the concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
$CL^{a,b}$	Systemic clearance	$Dose/AUC_{inf}$
$V_{ss}^{a,b}$	Steady-state volume of distribution following IV infusion	$V_{ss}=CL \times [MRT-(infusion\ time/2)]$ where MRT is the Mean Residence Time and is calculated as $AUMC_{inf}/AUC_{inf}$

a. If data permit
b. PF-07304814 only

PK samples will be stored and may be used in the future for CCI [redacted] CCI [redacted] scientific purpose, as needed.

9.3.1.3. Derivation of Pharmacokinetic Parameters (Urine)

Data permitting, following urine parameters will be calculated.

Parameter	Definition	Method of Determination
Total [^{14}C] Urine	Total cumulative [^{14}C] excreted into urine from time zero to the time of last measurable concentration following intravenously administered [^{14}C] PF-07304814 microtracer dose	Directly from observed [^{14}C] data
% [^{14}C] Urine	% of [^{14}C] in the urine following IV administration expressed as a percent of the [^{14}C] dose administered	(Total [^{14}C] Urine/[^{14}C] $Dose_{iv}$) *100 where, [^{14}C] $Dose_{iv}$ is [^{14}C] intravenously administered dose of [^{14}C] PF-07304814
Ae (PF-00835231)	Amount of unchanged drug excreted in urine	Sum of [PF-00835231 urine concentration * sample volume] for each collection interval
Ae% (PF-00835231)	Percent of PF-00835231 recovered unchanged in urine	Ae/Dose*100

Total urine [^{14}C] concentrations and percent [^{14}C] will be listed and summarized using descriptive statistics. Individual and summary profiles of urine [^{14}C] will be graphically presented.

9.3.1.4. Metabolic Profiling and Metabolite Identification

Plasma, urine, and fecal samples will be analyzed for identification of metabolites of PF-07304814, if possible. Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized in the CSR.

9.3.2. Other Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, and safety laboratory data 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.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. 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 will not be required to be reported, unless otherwise noted. Demographic data (including participant race, ethnicity, age, and gender) collected at screening will be reported.

9.3.2.1. 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 postdose 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

9.3.3. Other Analyse(s)

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

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development.

9.5. Sample Size Determination

A sample size of 4 participants is considered the minimum sample size for mass-balance/ADME studies which include assessment of metabolic profiling. The sample size is not based on empirical data or hypothesis testing criteria. Approximately 5 participants will be enrolled to study intervention such that approximately 4 evaluable participants complete the study with completed collections of plasma, urine, and fecal samples.

If the number of fully evaluable participants falls below 4, participants may be replaced.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant 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, privacy and data protection 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 on which 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 15 days from the previous ICD signature date.

10.1.4. Data Protection

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

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

submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

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

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

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the clinical monitoring plan , which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

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

10.1.9. Study and Site Start and Closure

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

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

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

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

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

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

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

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

10.1.10. Publication Policy

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

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

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

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

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

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

10.1.11. Sponsor's Qualified Medical Personnel

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 2. 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) PT/INR/APTT	BUN and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein eGFR[a]	Local Dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and Culture[b]	COVID-19 testing Urine drug testing Urine cotinine testing Urine alcohol testing At screening only: • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus • FSH (females only)

a. eGFR will be calculated using equations below.
b. At PI discretion.

CKD-EPI equation:

- If female and SCr is ≤0.7 mg/dL:

  GFR (mL/min/1.73 m^2) = 144 × (SCr/0.7) – 0.329 × 0.993age (× 1.159, if Black).

- If female and SCr is >0.7 mg/dL:

  GFR (mL/min/1.73 m^2) = 144 × (SCr/0.7) – 1.209 × 0.993age (× 1.159, if Black).

- If male and SCr is ≤0.9 mg/dL:

  GFR (mL/min/1.73 m^2) = 141 × (SCr /0.9) – 0.411 × 0.993age (× 1.159, if Black).

- If male and SCr is >0.9 mg/dL:

  GFR (mL/min/1.73 m^2) = 141 × (SCr /0.9) – 1.209 × 0.993age (× 1.159, if Black).

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.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of CCI or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

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

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

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

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

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

Follow-Up of AEs and SAEs

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

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

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

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

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not a WOCBP (see definitions below in Section 10.4.3).

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

6. 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.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07304814 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

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

- The samples will be retained as indicated:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs

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

ECG Findings That <u>May</u> Qualify as SAEs

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

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (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: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activities of daily living
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
APTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the concentration-time profile from time 0 to 24 hours
AUC_{inf}	area under the concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the concentration-time profile from time 0 to the time of the last quantifiable concentration
$AUMC_{inf}$	the area under the first moment curve from time 0 extrapolated to infinite time
AV	atrioventricular
BBS	Biospecimen Banking System
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C_{24}	observed plasma concentration at 24 hours
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology collaboration
CL	systemic clearance
C_{last}	predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form

Abbreviation	Term
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DVT	deep venous thrombosis
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IBS	irritable bowel syndrome
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IND	Investigational New Drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board

Abbreviation	Term
IV	intravenous
K_{el}	terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
LBBB	left bundle branch block
LFT	liver function test
Log_e	natural logarithm
LPLV	last participant last visit
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MRT	mean residence time
msec	millisecond
MTD	maximum tolerated dose
N/A	not applicable
NHP	nonhuman primate
NOAEL	no-observed-adverse-effect level
PCR	polymerase chain reaction
PCRU	Pfizer clinical research unit
PD	pharmacodynamic(s)
PE	physical exam
pH	negative log of the hydrogen ion concentration
PI	principal investigator
PK	pharmacokinetic(s)
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction/complex
QA	quality assurance
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAI	site administration instructions
SAP	Statistical Analysis Plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SoC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SToD	Study Team on Demand

Abbreviation	Term
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TA	technical agreement
TBili	total bilirubin
TEAE	treatment emergent adverse event
T_{max}	time for C_{max}
ULN	upper limit of normal
US	United States
V_{ss}	steady-state volume of distribution following IV infusion
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

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