Title Page

A PHASE 1, OPEN-LABEL, RANDOMIZED, SINGLE DOSE, CROSSOVER STUDY TO ESTIMATE THE RELATIVE BIOAVAILABILITY OF PF-07817883 FOLLOWING ORAL ADMINISTRATION OF NEW FORMULATIONS RELATIVE TO THE REFERENCE FORMULATION IN HEALTHY ADULT PARTICIPANTS UNDER FASTED CONDITION

Study Intervention Number:	PF-07817883
Study Intervention Name:	NA
US IND Number:	162644
EU CT Number:	2023-506442-24-00
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5091013
Phase:	Phase 1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A study to learn how PF-07817883 is taken up into the blood of healthy adults after taking tablets of study drug with varying ingredients.

Document History

Document	Version Date
Original protocol	24 August 2023

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Open-Label, Randomized, Single Dose, Crossover Study to Estimate the Relative Bioavailability of PF-07817883 Following Oral Administration of New Formulations Relative to The Reference Formulation in Healthy Adult Participants Under Fasted Condition

Brief Title: A study to learn how PF-07817883 is taken up into the blood of healthy adults after taking tablets of study drug with varying ingredients.

Regulatory Agency Identification Number(s):

US IND Number:	162644
EU CT Number:	2023-506442-24-00
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5091013
Phase:	Phase 1

Rationale:

PF-07817883 is a potent and selective inhibitor of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M^{pro}) that is currently being developed as an oral treatment of coronavirus disease 2019 (COVID-19).

The purpose of this study is to estimate the oral bioavailability of 3 new formulations of PF-07817883 (test) relative to reference tablet formulation in healthy adult participants under fasted conditions. The study will also assess the safety and tolerability of test and reference tablet formulations in healthy adult participants.

Results from this study will inform the selection of formulation for subsequent studies in the development program.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To determine the oral bioavailability of test oral formulations of PF-07817883 relative to the reference oral formulation.	• C_{max} and AUC_{inf} if data permit, otherwise AUC_{last}.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-07817883 formulations in healthy participants.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.

Abbreviations: AUC_{inf}=area under the plasma concentration-time profile from time 0 extrapolated to infinity, AUC_{last}=area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration, C_{max}=maximum observed concentration, ECG=electrocardiogram, TEAE=treatment emergent adverse event.

Overall Design:

This is a Phase 1, open-label, randomized, 4-period, 4-sequence crossover study in healthy adult participants evaluating the oral bioavailability of 3 new PF-07817883 test oral formulation(s) compared to PF-07817883 reference oral formulation.

Number of Participants:

Approximately 12 participants will be enrolled in the study in order to have at least 8 completers.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

1. Male and female participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and ECG.
2. Body mass index (BMI) of 16 to 32 kg/m^2; and a total body weight >45 kg.
3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
4. Capable of giving signed informed consent.

Exclusion Criteria

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

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).

- Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

- History of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HBsAg), or hepatitis C antibody (HCVAb). Hepatitis B vaccination is allowed.

2. Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior, laboratory abnormality, or other conditions and situations that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

3. Positive test result for SARS-CoV-2 infection at admission.

4. 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 with the exception of moderate/strong CYP3A inducers or time-dependent inhibitors which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention.

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

6. Screening supine blood pressure (BP) ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of supine rest. If systolic BP is ≥140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, 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.

7. Standard 12-lead ECG (single) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTc corrected using Fridericia's formula [QTcF] >450 ms, complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-segment and T-wave [ST-T] interval changes suggestive of myocardial ischemia, second- or third- degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias). If QTcF exceeds 450 ms, or a combination of three of the graphical deflections seen on a typical electrocardiogram (QRS) exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to

determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

8. 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:

   - Aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level >1.5 × upper limit of normal (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.

9. 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).

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

Study Arms and Duration:

Study Intervention(s)	
Intervention Name	PF-07817883
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	All test formulations and the reference formulation are immediate release tablets and expected have similar performance. All tablet formulations are of 300 mg unit strength.
Unit Dose Strength(s)	300 mg/tablet
Route of Administration	Oral

Abbreviations: AxMP= auxiliary medicinal product, IMP= investigational medicinal product, NIMP=non-investigational medicinal product.\

Study Arm(s)				
Arm Title	A	B	C	D
Arm Description	Participants will receive 300 mg SD of reference formulation on Day 1 of the treatment period	Participants will receive 300 mg SD of test formulation 1 on Day 1 of the treatment period	Participants will receive 300 mg SD of test formulation 2 on Day 1 of the treatment period	Participants will receive 300 mg SD of test formulation 3 on Day 1 of the treatment period

Abbreviation: SD=single dose.

Statistical Methods:

A sample size of approximately 12 participants with 8 completers was chosen to provide adequate precision to compare the relative bioavailability of test formulations of PF-07817883 relative to the reference formulation in Periods 1 through 4.

For the primary objective, natural log transformed AUC_{inf} (if data permit), AUC_{last} (otherwise), and C_{max} for PF-07817883 will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect in Periods 1 to 4. Estimates of the adjusted mean differences (test-reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% confidence intervals for the ratios. Treatment A will be the Reference treatment while Treatments B, C, and D will be the test treatments.

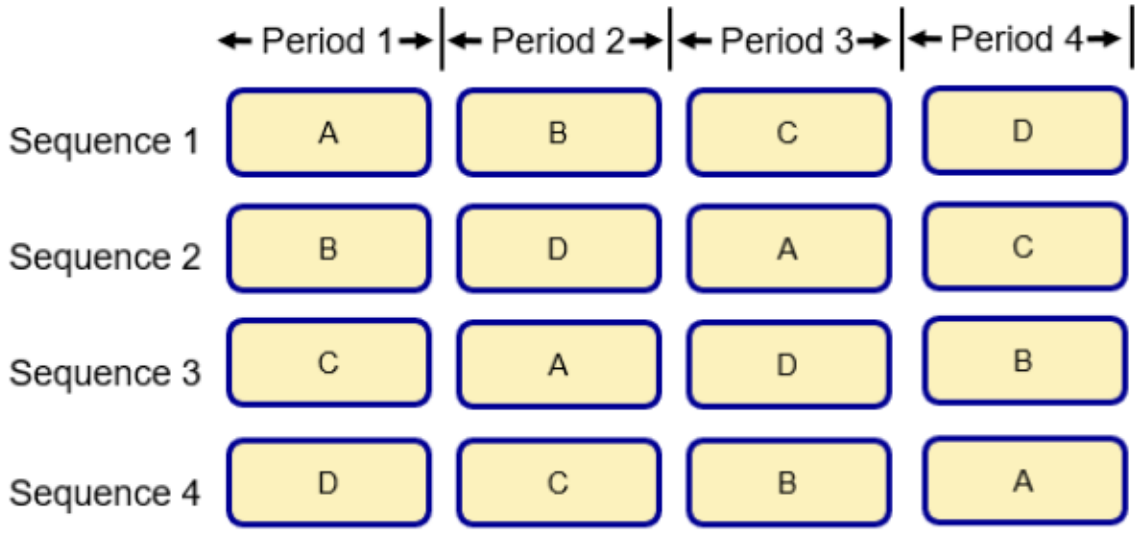
All safety analyses will be performed on the safety population. Adverse events (AEs), ECGs, vital signs, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, and vital sign abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Plasma pharmacokinetic (PK) parameters to be summarized descriptively.

Ethical Considerations:

PF-07817883 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate PK, safety and tolerability data for further clinical development.

1.2. Schema

Figure 1. Schema



DMID, lot numbers:
A: DP-006067, 23-DP-01449
B: DP-006067, 23-DP-01526
C: DP-006973, 23-DP-01687
D: DP-006974, 23-DP-01696

1.3. Schedule of Activities

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

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

Table 1. Schedule of Activities

Visit Identifier Abbreviations used in this table may be found in Section 10.9	Screening		For each of Period 1-4									FU	ET	Notes
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1							Day 2	Day 3	28-35 days		• F/U activities only in the last period. • F/U may occur via telephone contact, must occur 28-35 days after the final dose of study intervention. • Day -1 activities only before Period 1 Day 1.
Planned hours Post dose			0	0.5	1	2	4	6	8	12	24	48			
Informed consent	X													
Inclusion/exclusion criteria	X	X												• Period 1 only
CRU Confinement		X	→	→	→	→	→	→	→	→	→	X			
Medical/medication history (update)	X	X												
Demography (including weight and height)	X													• Refer to Section 8.1.1.2
Contraception check	X	X										X	X	X	• Day 3 performed only at discharge from CRU
12-lead ECG (single)	X		X									X		X	• Day 1 performed pre-dose • Day 1 not required in Periods 2-4 • Day 3 only in last period
Vital signs (BP/PR)	X		X									X		X	• Day 1 performed pre-dose • Day 3 only in the last period • Refer to Section 8.3.1

Table 1. Schedule of Activities

Visit Identifier Abbreviations used in this table may be found in Section 10.9	Screening		For each of Period 1-4									FU	ET	Notes
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1							Day 2	Day 3	28-35 days		• F/U activities only in the last period. • F/U may occur via telephone contact, must occur 28-35 days after the final dose of study intervention. • Day -1 activities only before Period 1 Day 1.
Planned hours Post dose			0	0.5	1	2	4	6	8	12	24	48			
COVID-19 test/ procedures	X	X												• COVID-19 test to meet inclusion on admission. Other COVID-19 related procedures per local regulations.
PE	X	X											X	• PE will be performed at screening or admission. • PE at ET visit only at PI's discretion
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	X	X	
Urine sample for:															
Urine drug testing	X	X													• Not required in Periods 2-4
Urinalysis	X	X										X		X	• Day 3 in last period only
Blood sample for:															
Safety laboratory (≥4h fasting)	X	X										X		X	• Day 3 in last period only.
Serum FSH (post-menopausal females only)	X														
Pregnancy test (WOCBP only)	X	X										X		X	• Day 3 performed only at discharge from the CRU.
Serology: HBsAg, HBsAb, HBcAb, HCVAb, and HIV	X														
PK plasma sampling for PF-07817883			X	X	X	X	X	X	X	X	X	X		X	• The sample at 0h will be the pre-dose PK sample. • 48h PK sample in Periods 1 to 3 will be considered 0h PK sample for the subsequent period.

Table 1. Schedule of Activities

Visit Identifier Abbreviations used in this table may be found in Section 10.9	Screening		For each of Period 1-4									FU	ET	Notes
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**							**Day 2**	**Day 3**	**28-35 days**		• F/U activities only in the last period. • F/U may occur via telephone contact, must occur 28-35 days after the final dose of study intervention. • Day -1 activities only before Period 1 Day 1.
Planned hours Post dose			**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**48**			
Administration of study intervention:														
PF-07817883 dosing			X											• See Section 5.3.2 Meals and Dietary Restrictions
Other assessments:														
Drug product acceptability Questionnaire			X											• The assessment will be administered immediately after the dose in each period (see Appendix 8).

2. INTRODUCTION

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

2.1. Study Rationale

The purpose of this study is to estimate the oral bioavailability of 3 new tablet formulations of PF-07817883 (test) relative to reference tablet formulation in healthy adult participants under fasted conditions. The study will also assess the safety and tolerability, of test and reference tablet formulations in healthy adult participants. Additionally, drug product acceptability will be explored for each of the formulations.

Results from this study will inform the selection of formulation for subsequent studies in the development program.

2.2. Background

2.2.1. Disease Overview

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

COVID-19 manifests as a wide range of illnesses, from asymptomatic infection to severe pneumonia, ARDS, and death. While the majority of cases (approximately 80%) are asymptomatic or mild,[2] patients who are hospitalized with COVID-19 may experience significant morbidity and mortality[3,4] and are at increased risk of developing comorbidities such as ARDS, acute cardiac injury, thromboembolic events, and/or kidney injury.[5-7]

2.2.2. Rationale for Development of PF-07817883

The coronavirus M^{pro} is a virally-encoded enzyme that is critical to the SARS-CoV-2 replication cycle, analogous to other obligatory virally-encoded proteases (eg, HIV protease or HCV protease). Mutagenesis experiments with other coronaviruses and picornaviruses that are related to SARS-CoV-2 (picornavirus-like supercluster) have demonstrated that the activity of M^{pro} is essential for viral replication. No close human analogs of coronavirus M^{pro} enzymes are known, suggesting that appropriate M^{pro} inhibitors may function as selective inhibitors of SARS-CoV-2 and other coronaviruses as therapeutic agents.

Inhibition of the SARS-CoV-2 M^{pro} by nirmatrelvir/ritonavir has demonstrated the efficacy of an antiviral in the reduction of hospitalization and death in mild to moderate COVID-19 patients with high risk of progression to severe disease. Despite the availability of nirmatrelvir/ritonavir some high-risk patients may be ineligible for nirmatrelvir/ritonavir due to DDIs, and remdesivir may be inaccessible for some patients as it requires IV administration in a healthcare setting and returning for three subsequent days for additional daily IV dosing. There remains an important need for additional safe and effective therapeutic interventions that do not require administration in a healthcare setting, are not

limited by DDIs, and have a risk/benefit profile supportive of administration to a broader patient population.

2.2.3. Nonclinical Overview

PF-07817883 is a potent (IC_{50} = CCI μM; K_i = CCI μM) and selective inhibitor of SARS-CoV-2 M^{pro}, exhibiting broad spectrum inhibitory activity across the Coronaviridae family of M^{pro} enzymes. The in vitro antiviral activity of PF-07817883 against SARS-CoV-2 was demonstrated in several cell lines. In all cellular systems tested, PF-07817883 demonstrated potent antiviral activity against SARS-CoV-2. PF-07817883 also exhibited antiviral efficacy against SARS-CoV-1, HCoV-229E, and MERS-CoV in cellular systems. CCI [redacted]

More details are presented in the current IB.

2.2.4. Biopharmaceutics and Nonclinical Pharmacokinetics

2.2.4.1. Biopharmaceutics

PF-07817883 is a neutral compound exhibiting moderate aqueous apparent solubility in various bio-relevant media and low passive permeability. In a preliminary passive permeability assessment in the RRCK cell line, PF-07817883 exhibited an A-B P_{app} of 0.50×10^{-6} cm/s, indicating low passive permeability.

2.2.4.2. Nonclinical Pharmacokinetics and in vitro Metabolism

PF-07817883 exhibited low in vitro permeability and preferentially distributed into plasma relative to blood cells. PF-07817883 exhibited a low to moderate CL, with a moderate to low V_{ss} resulting in $t_{½}$ values of approximately 10 hours in rats and 2.8 hours in monkeys. Following oral dosing, PF-07817883 was rapidly absorbed with moderate bioavailability in rats and monkeys. In rat and monkey repeat dose toxicity studies, mean systemic exposures increased with increasing dose and no consistent sex-related differences were observed.

Concentration-dependent plasma protein binding was observed in rabbits and monkeys, while no meaningful concentration-dependent binding was observed in humans at ≤10 μM (CCI [redacted]. PF-07817883 distributed into the liver and lung to a greater extent than other tissues, while distribution into the brain was limited. CCI [redacted]

CYP-mediated oxidation was the primary metabolic route of PF-07817883 in vitro and in rats. In vitro studies in human liver microsomes indicated metabolism of PF-07817883 was predominantly mediated by CYP3A4 (CCI [redacted]).

In accordance with FDA and EMA DDI guidance, CCI [redacted]

More details are presented in the current IB.

2.2.5. Toxicology of PF-07817883

PF-07817883 was assessed in a series of nonclinical studies.

The toxicity of PF-07817883 was evaluated in CCI [redacted] GLP toxicity studies CCI [redacted] There were no adverse findings in any of the studies. The NOAELs in the CCI [redacted] studies CCI [redacted]

In general, the non-adverse findings in the non GLP exploratory studies and the GLP pivotal studies were similar. CCI [redacted]

CCI [redacted]

In embryo-fetal development studies, PF-07817883 was orally administered during organogenesis to pregnant rats and rabbits at doses of 100, 300, or 1000 mg/kg/day on GD 6-17 (rats) or GD 7-19 (rabbits). In the rat, there were no PF-07817883-related effects up to the highest dose of 1000 mg/kg/day. Unbound systemic exposures at the NOAEL (1000 mg/kg/day) in this study were 598 µg•h/mL and 92.6 µg/mL for AUC_{24} and C_{max}, respectively. In the rabbit, there was no PF-07817883-related effect on fetal morphology or embryo-fetal viability up to the highest dose of 1000 mg/kg/day. However, lower fetal body weights were observed at 1000 mg/kg/day in the presence of non-adverse effects on maternal body weight and food consumption, resulting in a developmental NOAEL of 300 mg/kg/day. Unbound systemic exposures at 300 mg/kg/day in this study were 145 µg•h/mL and 44 µg/mL for AUC_{24} and C_{max}, respectively. In the combined male/female fertility study in Wistar Han rats, there were no PF-07817883-related effects up to the highest dose of 1000 mg/kg/day.

More details are presented in the current IB.

2.2.6. Clinical Overview

As of the date of this protocol, PF-07817883 is being evaluated in 3 Phase 1 studies (C5091001, C5091008 and C5091014) and 1 Phase 2 study (C5091003) in COVID-19 patients.

The ongoing study C5091001 is a multipart study in healthy adult participants to evaluate the safety, tolerability and PK of PF-07817883. PK of PF-07817883 was evaluated in PART-1:SAD, PART-2:MAD, PART-4:ME and PART-5:DDI of an ongoing C5091001 study. PART-5:DDI evaluated the effect of PF-07817883 on midazolam PK. In addition, PK of PF-07817883 in Japanese and non-Japanese population was compared in PART-5:DDI. The doses ranged between 150-4000 mg and 200-1500 mg in SAD and MAD, respectively. In MAD steady state PF-07817883 PK was evaluated after 10 days of BID dosing. In PART-4:ME 600 mg PF-07817883 SD was administered to healthy adult participants. PART-5 evaluated the effect of repeat dosing of PF-07817883 on the PK of SD midazolam. In PART-6, effect of supratherapeutic exposures on safety, tolerability, and QTc is being assessed at an oral dose of 6000 mg (given as 2 doses of 3000 mg at 0 and 1 hr).

C5091008 is an ongoing Phase 1, open-label, 2 period, fixed sequence study to estimate the effect of itraconazole (a strong CYP3A4 inhibitor) on the PK of PF-07817883 in healthy participants. Study C5091014 will evaluate the effect of hepatic impairment on the single dose PK of PF-07817883, respectively.

The details of design, objectives and endpoints are detailed in the current IB.

2.2.6.1. Summary of PF-07817883 Pharmacokinetics in Humans

CCI

CCI [redacted]

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

2.2.6.2. Safety Overview

The preliminary data collected in Study C5091001, as of the data snapshot (18 January 2023) in PART-1 and PART-2 of the Phase 1 study (C5091001), demonstrated an acceptable safety profile at SDs of PF-07817883 or placebo ranging from 150 mg to 4000 mg in PART-1, and at doses of 200 mg to 1500 mg BID of PF-07817883 or placebo for 10 days in PART-2. Dose escalation stopping rules were not triggered and MTD was not achieved. There have been no deaths, SAEs or SUSARs reported. CCI [redacted] Preliminary results from PART-6 show acceptable safety and tolerability of PF-07817883 in healthy adult volunteers at the dose of 6000 mg. According to preliminary safety results from C5091008; a total of 12 healthy adults were enrolled and completed the study. A total of 11 adverse events occurred in 4 participants, all of which were mild.

CCI [redacted]

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

2.3. Benefit/Risk Assessment

PF-07817883 is not expected to provide any clinical benefit to healthy participants. The purpose of this study is to estimate the rBA of PF-07817883 in 3 to 4 test tablet formulations relative to reference tablet formulation in healthy adult participants under fasted condition.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07817883 may be found in the current IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

2.3.1. Risk Assessment

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

2.3.2. Benefit Assessment

For healthy participants in this study, no clinical benefit is expected.

2.3.3. Overall Benefit/Risk Conclusion

PF-07817883 is not expected to provide any clinical benefit to healthy participants in this study.

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with PF-07817883 are justified by the anticipated benefits that may be afforded to participants with COVID-19 in future.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To determine the oral bioavailability of test oral formulations of PF-07817883 relative to the reference oral formulation.	• C_{max} and AUC_{inf} if data permit, otherwise AUC_{last}.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-07817883 formulations in healthy participants.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To characterize the PK of PF-07817883 after single oral dose of PF-07817883 formulations.	• Plasma PK parameters: T_{max}, C_{12}, and if data permit V_z/F, CL/F and $t_{½}$.
• To assess the drug product acceptability of PF-07817883 formulations.	• Assessment of drug product acceptability via a questionnaire.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, randomized, 4-period, 4-sequence crossover study in healthy adult participants evaluating the rBA of 3 new PF-07817883 test oral formulation(s) compared to PF-07817883 reference oral formulation. Approximately 12 participants will be enrolled in this study with approximately equal number of participants randomized to 1 of 4 sequences (Table 2). The new formulations used for each treatment as defined in Table 2 will be decided based on the availability of new formulations.

Table 2. Study Design

Sequence	Period 1	Period 2	Period 3	Period 4
1 (n=3)	A	B	C	D
2 (n=3)	B	D	A	C
3 (n=3)	C	A	D	B
4 (n=3)	D	C	B	A

Treatment A = PF-07817883 300 mg reference formulation, fasted, DP-006067, 23-DP-01449
Treatment B = PF-07817883 300 mg test formulation 1, fasted, DP-006067, 23-DP-01526
Treatment C = PF-07817883 300 mg test formulation 2, fasted, DP-006973, 23-DP-01687
Treatment D = PF-07817883 300 mg test formulation 3, fasted, DP-006974, 23-DP-01696

Healthy participants will be screened to determine eligibility within 28 days prior to study treatment. Participants will report to the CRU on Period 1 Day -1 (Study Day -1) and will be required to stay at the CRU until discharge. The participants will remain confined at the CRU until all assessments in all periods are complete.

In each period on Day 1, following an overnight fast of ~10h, participants will receive one of the treatments as defined in Table 2. Serial plasma PK samples will be collected up to 48 hours following the dose, at times outlined in the SoA. Participants will also complete a drug-product acceptability questionnaire shortly after receiving PF-07817883 in each period. At least 48 hours of washout between the doses of PF-07817883 administered to a participant in consecutive periods will be implemented. Dosing in the subsequent periods can take place immediately following the last PK sample collection of a period (SoA, Section 5.3).

A follow-up (which may be a phone call) will be made to participants approximately 28 to 35 days from administration of the final dose of study intervention.

4.2. Scientific Rationale for Study Design

This study will evaluate bioavailability of 3 new tablet formulations (test) of PF-07817883 relative to the current formulation (reference) in healthy participants.

Based on the median half-life of [CCI] hr, observed in C5091008 study, which also used 300 mg immediate release tablet formulation as a SD; the [CCI] hr washout interval is deemed sufficient to provide the concentration <5% of C_{max} in the subsequent period.

In study C5091001, administration of PF-07817883 oral suspension with high-fat meal decreased AUC_{last} and C_{max} by [CCI]% and [CCI]%, respectively. Thus, to avoid the potential effect of food on PF-07817883 PK, the participants will be dosed in fasted state in all periods.

Drug product acceptability questionnaire is an exploratory endpoint to inform the future product development.

Based in the formulation, the test and reference formulations are expected to have a very similar safety profile. In order to limit the study-burden to a participant, post-dose safety labs/ECG are not proposed in each period.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for PF-07817883, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound and no evidence for severe manifestations of developmental toxicity in nonclinical studies at relevant clinical exposures for PF-07817883. Therefore, the use of a highly effective method of contraception may be required as outlined in Appendix 4.

4.3. Justification for Dose

A single oral dose of 300 mg will be used in this study. This dose has been selected based on available unit strength of the formulations, observed PK and safety in healthy participants in an ongoing study C5091001.

CCI [redacted]

PF-07817883 was safe and well tolerated in SAD up to 4000 mg dose and in MAD and up to 1500 mg BID for 10 days. Maximum tolerated dose was not achieved. CCI [redacted]. Therefore, a single dose of PF-07817883 at 300 mg is expected to be safe in healthy adult participants to be enrolled in this study.

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods of the study, including the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and ECG.

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

Other Inclusion Criteria:

2. BMI of 16 to 32 kg/m^2; and a total body weight >45 kg.

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

4. Capable of giving signed informed consent as described in day, 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).

   - Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

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

2. Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior, laboratory abnormality, or other conditions and situations that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

3. Positive test result for SARS-CoV-2 infection at admission.

Prior/Concomitant Therapy:

4. 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 with the exception of moderate/strong CYP3A inducers or time-dependent inhibitors which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

5. Participants who have received a COVID-19 vaccine within 7 days before screening or admission, or who are to be vaccinated with a COVID-19 vaccine at any time during the study confinement period.

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

7. A positive urine drug test. A single repeat for positive drug screen may be allowed.

8. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of supine rest. If systolic BP is ≥140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, 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.

9. Standard 12-lead ECG (single) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, 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 QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values 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.

10. 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 >1.5 × 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.
    - eGFR <60 mL/min/1.73 m^2 based on the CKD-EPI equation.

Other Exclusion Criteria:

11. 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).
12. Use of tobacco or nicotine containing products in excess of the equivalents of 5 cigarettes per day or 2 chews of tobacco per day.
13. Unwilling or unable to comply with the criteria in the Lifestyle Considerations Section 5.3 of this protocol.
14. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.
15. History of sensitivity reactions to PF-07817883 or any of the formulation components of PF-07817883.
16. Pregnant or breastfeeding women.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the

donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. 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 morning dose in each period.
- Water is permitted until 1 hour prior to study intervention administration in each period. Water may be consumed without restriction beginning 1 hour after PF-07817883 dosing. Noncaffeinated drinks (except red wine, 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 PF-07817883 dosing.
- Dinner will be provided approximately 9 to 10 hours after PF-07817883 dosing.
- An evening snack may be permitted.
- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) 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.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products within 2 hours of vitals/ ECG measurements and dosing.
- Participants will abstain from alcohol for 24 hours prior to admission (or as specified above for red wine) to the CRU and continue abstaining from alcohol until collection

of the final PK sample. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.4. 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;

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, PR, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after PF-07817883 dosing.

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

For the purposes of this protocol, study intervention refers to PF-07817883.

6.1. Study Intervention(s) Administered

Study Intervention(s)	
Intervention Name	PF-07817883
Type	Drug
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	All test formulations and the reference formulation are immediate release tablets and expected have similar performance. All tablet formulations are of 300 mg unit strength.
Unit Dose Strength(s)	300 mg/ tablet

Study Intervention(s)	
Dosage Level(s)	300 mg single dose per treatment, per period.
Route of Administration	Oral
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in bulk. CRU staff will prepare individual doses for administration. Each dose container will be labeled as required per country requirement.
SRSD	IB for PF-07817883
Current/Former Name(s) or Alias(es)	PF-07817883

Study Arm(s)				
Arm Title	A	B	C	D
Arm Description	Participants will receive 300 mg SD of reference formulation on Day 1 of the treatment period	Participants will receive 300 mg SD of test formulation 1 on Day 1 of the treatment period	Participants will receive 300 mg SD of test formulation 2 on Day 1 of the treatment period	Participants will receive 300 mg SD of test formulation 3 on Day 1 of the treatment period
DMID, Lot	DP-006067, 23-DP-01449	DP-006067, 23-DP-01526	DP-006973, 23-DP-01687	DP-006974, 23-DP-01696

PF-07817883 will be supplied by Pfizer as 300-mg tablets.

Tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

6.1.1. Administration

Study interventions will be administered orally and according to the conditions described in the SoA section and Protocol Section 5.3.2.

On the dosing day (Day 1) in each period, following an overnight fast of at least 10 hours, participants will receive one of the PF-07817883 300 mg formulations as per the randomization sequence administered orally in the morning.

Investigator site personnel will administer study intervention with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG

measurements), eating, and drinking beverages other than water during the first 4 hours after dosing in addition to other specifications detailed in Section 5.3.

Administration of study intervention(s) at the site will be performed by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

Following administration of study intervention(s) at the site, participants will be observed for 1 hour by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study

interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the CRU's local/site procedures. 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.

Tablets will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Assignment to Study Intervention

The investigator 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. Blinding

This is an open label study.

6.5. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

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. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.6. Dose Modification

No dose modification is anticipated.

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

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

6.8. Treatment of Overdose

For this study, any dose of PF-07817883 greater than CCI mg within a 24-hour time period ±2 hours will be considered an overdose.

There is no specific treatment for an overdose

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

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

6.9. Prior and Concomitant Therapy

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 with the exception of moderate/strong CYP3A inducers or time-dependent inhibitors which are prohibited within 14 days plus 5 half-lives 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.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

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.

6.9.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07817883. 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. Reasons for permanent discontinuation of study intervention include the following:

- AE requiring discontinuation in investigator's view;
- Pregnancy.

If study intervention is permanently 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. Potential Cases of Acute Kidney Injury

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

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

Follow-up Assessments

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results.

Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals.

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR, eCrCl and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Appendix 6.

Assessments of urine albumin-to-creatinine ratio or urine volume may also be performed as appropriate.

If appropriate, nephrology consultation may be recommended to facilitate differentiation of renal parenchymal disease, pre-renal azotemia, and post-renal obstruction.

Differentiating Acute Kidney Injury from DICI

A confirmed Screat increase is defined as:

(i) ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR

(ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Based on the assessments performed, suspected AKI (including DIKI) may be differentiated from DICI as follows.

Adult participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys AND Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.
eGFR	Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available)	
Albuminuria or proteinuria	Confirmed albuminuria increase (see Appendix 6 for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either there is (i) new-onset or worsening albuminuria or proteinuria are detected.

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

7.1.2. ECG Changes

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

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

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

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

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

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 28 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 28 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 samples, may not need to be repeated, 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 make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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.

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 270 mL. The actual collection times of blood sampling may change. Additional blood

samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

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

8.1.1. Baseline Procedures

8.1.1.1. Medical History

A detailed medical history will be reviewed and recorded at screening and updated on admission. This will include detailed medical history as well as a history of prior illegal drug, alcohol, and tobacco use within 60 days prior to enrollment. If the participants are discharged between the periods, medical history may be updated.

8.1.1.2. Demographics

Participants' race, ethnicity, age, gender, height, and weight will be recorded at screening.

8.2. Efficacy Assessments

Efficacy parameters are not evaluated in this study.

8.3. Safety Assessments

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

8.3.1. Vital Signs

8.3.1.1. Blood Pressure and Pulse Rate

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. 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.

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

8.3.2. 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 record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3. Electrocardiograms

Standard 12-lead ECGs will be collected at times specified in the SoA section of this protocol using an ECG system that automatically calculates the HR and measures PR, QT, QTcF, and QRS intervals. 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 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

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

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

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

8.3.4. 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 significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 48 hours after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

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

See Appendix 5 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 6 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

8.3.5. COVID-19 Specific Assessments

COVID-19 related procedures as per the SoA and local regulations. Additional testing may be required by the PI.

8.3.6. Pregnancy Testing

A urine or serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to starting the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

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

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental

exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.

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

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form. 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 report 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 report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal

demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOP.

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.4.1 through 8.4.4. 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.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s), are recorded on the AE page of the CRF.

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

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

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide approximately 1.5 mL of plasma, will be collected for measurement of plasma concentrations of PF-07817883 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 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 will be used to evaluate the PK of PF-07817883. Samples collected for analyses of PF-07817883 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. The exploratory results may not be reported in the CSR.

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

Samples collected for measurement of plasma concentrations of PF-07817883 will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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

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 deviation. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

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

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

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

8.10. Drug Product Acceptability Questionnaire

The acceptability attributes of PF-07817883 will be evaluated by the participant using a Drug Product Acceptability Questionnaire (Appendix 8). In each period, each participant will complete the Drug Product Acceptability Questionnaire immediately following dosing. All efforts will be made to initiate the questionnaire immediately following dosing; however, it will not be captured as a protocol deviation, as long as the exact time of assessment is noted on the source document and the CRF.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention.
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention in at least one treatment period. Participants will be analyzed according to the product they actually received.
PK Concentration analysis set	The PK concentration population is defined as all participants randomized and treated who have at least 1 concentration value in at least 1 treatment period.
PK Parameter analysis set	The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PK parameters of interest in at least 1 treatment period.

9.3. Statistical Analyses

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

9.3.1. General Considerations

All data will be presented by treatment groups and by total. Descriptive statistics will be provided. The following listing of individual participants data may also be produced: Disposition Events, Potentially Important Protocol Deviations, Subject Evaluation Groups, Demographic Information, Concomitant Medications, Compliance with Study Intervention.

9.3.2. Primary Endpoint(s) Analysis

9.3.2.1. Definition of Endpoint(s)

The primary endpoints are the plasma PK endpoints C_{max} and AUC_{inf} (if data permits) otherwise AUC_{last}.

The analyses for the primary endpoints are described in Section 9.3.2.2.

9.3.2.2. Main Analytical Approach

Plasma PK parameters of PF-07817883 will be derived (as data permit) from the concentration-time data using standard noncompartmental methods as outlined in Table 3. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 3. Plasma PF-07817883 PK Parameters Definitions

Parameter	Definition	Method of Determination
AUC_{inf}*	Area under the concentration-time curve from time 0 extrapolated to infinity	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last}* is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis
AUC_{last}[a]	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
C_{max}	Maximum observed concentration	Observed directly from data
C_{12}	Concentration observed at 12 hours	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$*	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve. Only those data points judged to describe the terminal loglinear decline will be used in the regression.
CL/F*	Apparent clearance	$Dose/AUC_{inf}$
V_z/F*	Apparent volume of distribution	$Dose/(AUC_{inf} \cdot k_{el})$

*If data permit.
a. 48h PK sample in Periods 1 to 3 will be considered 0h PK sample for the subsequent period.

9.3.2.2.1. Statistical Methods for PK data

For the primary objective, natural log transformed AUC_{inf} (if data permit), otherwise AUC_{last}, and C_{max} for PF-07817883 will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect in Periods 1 to 4. Estimates of the adjusted mean differences (test-reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% confidence intervals for the ratios. Treatment A will be the Reference treatment while Treatments B, C, and D will be the Test treatments.

PK parameters, including plasma AUC_{inf} (if data permit), AUC_{last}, C_{max}, and T_{max}, $t_{½}$ (if data permit) of PF-07817883 will be summarized descriptively by treatment. For AUC_{inf} (if data permit), AUC_{last}, and C_{max}, a listing of the individual participant ratios (test/reference) will be provided. Box and whisker plots for AUC_{inf} (if data permit), AUC_{last}, and C_{max}, will be plotted by treatment.

The plasma concentrations of PF-07817883 will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant, as well as mean and median profiles of the plasma concentration time data will be plotted by treatment using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and semi-log scales.

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

9.3.3. Secondary Endpoint(s) Analysis

The analyses for safety endpoints are described in Section 9.3.5.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

The analyses of the plasma PK parameters are described above in Section 9.3.2.2.

The item and domain scores from the drug-product acceptability questionnaire (Appendix 8) for each test formation and the reference formulation will be listed and descriptively summarized and appropriate plots may be generated.

The summary and analysis of the drug product acceptability questionnaire responses may or may not be reported in the CSR.

9.3.5. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, vital signs, 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, and vital sign 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 collected at screening will be reported.

9.3.5.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

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

9.3.6. Other Analyses

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

9.4. Interim Analyses

No 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 approximately 12 participants with at least 8 completers was chosen to provide adequate precision to compare the relative bioavailability of test formulations of PF-07817883 relative to the reference formulation in Periods 1 through 4, based on estimates of the within-participant standard deviations of CCI for $\log_e AUC_{inf}$, CCI for $\log_e AUC_{last}$ and CCI for $\log_e C_{max}$. The expected widths of the 90% CIs with 80% coverage probability for the comparison of the test formulations of PF-07817883 relative to reference formulation are shown in Table 4 for a range of possible effects.

Table 4. Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects for AUC_{inf}, AUC_{last}, and C_{max}

CCI

A sufficient number of participants will be screened to achieve approximately 12 participants randomized to treatment sequence (3 per each sequence) such that there will be approximately 8 evaluable participants completing the study for an estimated total of 2 evaluable participants per sequence. Participants discontinuing for non-safety reasons may be replaced at the sponsor's discretion.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant 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 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 their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

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

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

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

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

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 10 days from the previous ICD signature date.

10.1.3. Data Protection

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

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

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

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

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

10.1.4. Committees Structure

10.1.4.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

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

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

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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 and/or paper form and are password-protected or secured in a locked room 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 records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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

10.1.7. Source Documents

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

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

Definition of what constitutes a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor's designee (Pfizer CRU).

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

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

10.1.8. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.9. Study and Site Start and Closure

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

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

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee 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. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the study contact list located in the CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol

and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant.

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; for example: calculation of estimated kidney function (ie, 2021 CKD-EPI eGFR). These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study

Table 5. Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) MCV MCH MCHC	Urea Creatinine Cystatin C[a] eGFR, eCrCl[b] Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[c]	COVID-19 testing Urine drug screening[e] Pregnancy test (β-hCG)[f] At screening: • FSH[d] • HBsAg • HBsAb[g] • HBcAb • HCVAb • HIV

a. Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (see Section 7.1.1).
b. Screening and Baseline eGFR or eCrCl is measured with Screat-based formula. Age-specific kidney function calculation (see Section 10.6.2) is recommended to assess presence or absence of post-baseline change in kidney function.
c. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
d. For confirmation of postmenopausal status only in females <60 years old and not using hormonal or HRT only.
e. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site- and study-specific).
f. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. See SoA for collection times.
g. Can be done either automatically or only if HBcAb or HBsAg is positive, as per local practices.

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 exploratory safety biomarkers 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 Meeting the AE Definition

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

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

10.3.2. Definition of an SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
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 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 using 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 EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study 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 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. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

- 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: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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.

Assessment of Causality

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

Follow-Up of AEs and SAEs

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

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

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

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

  OR

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

  OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
     - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years 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 highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

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.

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

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

    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*

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

    - Oral + barrier*
    - Injectable + barrier*

Sexual Abstinence

8. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: 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 T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), 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, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.6. Appendix 6: Kidney Safety: Monitoring Guidelines

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

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Obtaining Screening or Baseline Scys and postbaseline reflex Scys (if confirmed Screat increase ≥0.3 mg/dL) makes it feasible to distinguish AKI from DICI. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated:

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat only-based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat only-based equation (see Table 10.6.2.1) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat only-based eGFR and combined Screat plus Scys eGFR).

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

10.6.2. Age-Specific Kidney Function Calculation Recommendations

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

eGFR (mL/min/1.73m²)[8]

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

10.6.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria for adult participants.

KDIGO criteria grade (G)	Study Population	G1	G2	G3	G4	G5
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	Adult participants eGFR ($mL/min/1.73m^2$)	≥90	≥60 to 89	30 to 59	15 to 29	<15

KDIGO albuminuria (A) criteria	A1	A2	A3
Albumin-to-creatinine ratio (ACR)	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 ms.
• Absolute value of QTcF > 450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• New-onset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 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 asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

The major events of potential clinical concern listed above 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 is to be reported as AEs/SAEs.

10.8. Appendix 8: Drug Product Acceptability Questionnaire

Protocol ID: C5091013
Visit: _____

CENTER | PARTICIPANT ID
DATE OF VISIT: DD - MMM - YYYY

DRUG PRODUCT ACCEPTABILITY QUESTIONNAIRE
☐ (1) NOT DONE Language administered: ☒ English

Drug Product Acceptability Questionnaire

INSTRUCTIONS TO SITE: This questionnaire should be distributed to and filled out by participants immediately after having taken the study product on Day 1, each period.

Please ask the participant to view the tablets in the cup without touching them before ingesting the study product and before completing the questionnaire.

Please collect the questionnaire when complete. Please confirm that the questionnaire is complete. If there are missing items, please return the questionnaire to the participant and ask them to complete the missing items.

Please record the following information:

Study#/Study Site	
Period and Day	
Collect Date	
Collect Time	
Participant ID (Rand ID)	
Collected by	
Entered in PIMS by	
Checked in PIMS by	
Questionnaire Fully Completed (circle)	Yes/No

Protocol ID: C5091013
Visit: _____

CENTER | | | | | PARTICIPANT ID | | | | | | | | |
DATE OF VISIT | | | - | | | | - | | | | |
DD MMM YYYY

DRUG PRODUCT ACCEPTABILITY QUESTIONNAIRE
☐ (1) NOT DONE Language administered: ☒ English

Drug-Product Acceptability Questionnaire

Please tell us how much you agree or disagree with each of the following **14** statements by circling the number corresponding to your answer:

	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
1. The surface of the tablets looked rough (not smooth)	1	2	3	4	5
2. The tablets had an odd shape (not round, oval, or capsule-shaped)	1	2	3	4	5
3. The color of the tablets was not attractive	1	2	3	4	5
4. The tablets felt chalky or rough in my mouth	1	2	3	4	5
5. The tablets stuck to the inside of my mouth	1	2	3	4	5
6. The tablets felt waxy in my mouth	1	2	3	4	5
7. The tablets began to dissolve in my mouth before I swallowed them	1	2	3	4	5
8. The tablets tasted bitter	1	2	3	4	5
9. The tablets had a smell	1	2	3	4	5
10. When I took the tablets, I had a burning sensation in my mouth or on my tongue	1	2	3	4	5
11. When I took the tablets, I had a burning sensation in my throat	1	2	3	4	5
12. The tablets were too big to swallow	1	2	3	4	5
13. The tablets were difficult to swallow	1	2	3	4	5
14. Overall, these tablets were difficult to take	1	2	3	4	5

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
Abs	absolute
ACR	albumin-to-creatinine ratio
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC_{24}	area under the plasma concentration-time profile from time 0 to the time 24 hours
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinity
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
C_{12}	concentration at 12h nominal time post-dose
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL	total clearance of drug
CL/F	apparent clearance
C_{last}	last quantifiable concentration
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report

Abbreviation	Term
CT	clinical trial
CTIS	Clinical Trial Information System
CTMS	Clinical Trial Management System
CYP	cytochrome P450
CV	cardiovascular
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DMID	dosage material identification
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	US Food and Drug Administration
f_m	fraction metabolized
FSH	follicle-stimulating hormone
f_u	fraction unbound
F/U	follow-up
G1 to G5	KDIGO eGFR category standardization
GCP	Good Clinical Practice
GD	gestation day
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCoV-229E	human coronavirus 229E
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus

Abbreviation	Term
HR/hr	heart rate/hour (based on the content)
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	inhibitory concentration 50%
ICD	informed consent document
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous(ly)
K	Proportionality constant for Schwartz Equations (kidney function)
KDIGO	Kidney Disease Improving Global Outcomes
k_{el}	first-order elimination rate constant
Ki	inhibition constant
LBBB	left bundle branch block
LFT	liver function test
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
CCI [redacted]	
ME	Metabolism and Excretion
MERS-CoV	middle east respiratory syndrome coronavirus
M^{Pro}	main protease
MQI	medically qualified individual
MTD	maximum tolerated dose
NA	not applicable
NHP	non-human primates
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
CCI [redacted]	
PE	physical examination
PI	principal investigator
PIMS	Phase 1 Management System
PK	pharmacokinetic(s)
PR	pulse rate

Abbreviation	Term
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QRS	A combination of three of the graphical deflections seen on a typical electrocardiogram
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
rBA	relative bioavailability
RBC	red blood cell
RNA	ribonucleic acid
RR	resting rate
RRCK	Ralph Russ canine kidney cells RRCK
SAE	serious adverse event
SAD	single ascending dose
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SARS-CoV-2 M^{pro}	the main protease of SARS-CoV-2
Scr	serum creatinine
Screat	serum creatinine
Scys	serum cystatin C
SD	single dose
SDD	spray dried dispersion
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
ST-T	ST-segment and T-wave
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal half-life
T bili	total bilirubin
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
UV-Vis	ultraviolet-visible spectroscopy
V_{ss}	steady-state volume of distribution (=CL·MRT)
V_z/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

11. REFERENCES

1. WHO Situation Report 51. 11 March 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed: 29 March 2020.WHO Situation Report 51. 11 March 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed: 29 March 2020.

2. Wu Z, McGoogan J. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239-42.

3. Richardson S, Hirsch J, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323(20):2052-9.

4. Docherty A, Harrison E, Green C, et al. Features of 20-133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:1-12: m1985.

5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.

6. Pei G, Zhang Z, Peng J, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. J Am Soc Nephrol. 2020;31(6):1157-65.

7. Nopp S, Moik F, Jilma B, et al. Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Res Pract Thromb Haemost. 2020;4(7):1178-91.

8. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737-49.

Document Approval Record

Document Name:	C5091013 Protocol_24Aug2023
Document Title:	C5091013 Protocol_24Aug2023

Signed By:	Date(GMT)	Signing Capacity
PPD	24-Aug-2023 12:25:23	Author Approval
PPD	24-Aug-2023 19:05:48	Final Approval
PPD	24-Aug-2023 19:18:49	Business Line Approver