COVID-19: A MULTIPART, PHASE 1 STUDY WITH RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, SINGLE- AND MULTIPLE-DOSE ESCALATION TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-07817883 AND OPTIONAL OPEN-LABEL, RANDOMIZED STUDY TO EVALUATE RELATIVE BIOAVAILABILITY AND FOOD EFFECT OF SOLID ORAL FORMULATION AND OPTIONAL OPEN-LABEL, NON-RANDOMIZED STUDY TO EVALUATE METABOLISM AND EXCRETION OF PF-07817883 AND OPTIONAL RANDOMIZED, OPEN-LABEL STUDY TO ASSESS THE EFFECT OF PF-07817883 ON PHARMACOKINETICS OF MIDAZOLAM IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07817883
Study Intervention Name:	NA
US IND Number:	162644
EudraCT Number:	2022-002871-12
ClinicalTrials.gov ID:	NCT05580003
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5091001
Phase:	Phase 1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Multipart Phase 1 Study Including Single Ascending Dose, Multiple Ascending Dose, Relative Bioavailability, Food Effect, Metabolism and Excretion And Drug-Drug Interaction of PF-07817883 in Healthy Adult Participants

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Document History

Document	Version Date
Amendment 3	09 March 2023
Amendment 2	31 January 2023
Amendment 1	21 October 2022
Original protocol	14 September 2022

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

Protocol Amendment Summary of Changes Table

Amendment 3 (09 March 2023)

Overall Rationale for the Amendment: To include stopping criteria for sentinel dosing, increase sample size as well as for safety review of PART-6 as per comments received from FDA.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 Synopsis	Updated number of participants in PART-6 and in the overall study. Updated the statistical method for sample size justification.	To align the synopsis with the remainder of the protocol.	Substantial
Section 4.1.6 PART-6: SE	Stopping criteria for sentinel dosing as well as for safety review of PART-6 were added. Sample size was increased to 24 (4 in each of the 6 sequences) to improve power of demonstrating assay sensitivity.	To address comments received from FDA.	Substantial
Section 7.4 Stopping Criteria for PART-6: SE	Stopping criteria for sentinel dosing as well as for safety review of PART-6 were added.	To address comments received from FDA.	Substantial

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 9.5 Sample Size Determinatio; Section 9.5.6 PART-6:SE	Sample size was increased to 24 to improve power of demonstrating assay sensitivity.	To address comments received from FDA.	Substantial
Section 1.3.6. PART-6: SE	Notes in SoA (Table 9) were updated to clarify that contraception check and pregnancy test on Day -1 are scheduled for Period 1 only.	Clarification	Nonsubstantial

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

TABLE OF CONTENTS

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

LIST OF TABLES

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

COVID-19: A Multipart, Phase 1 Study with Randomized, Double Blind, Sponsor-Open, Placebo-Controlled, Single- and Multiple-Dose Escalation to Evaluate the Safety, Tolerability and Pharmacokinetics of PF-07817883 and Optional Open-Label, Randomized Study to Evaluate Relative Bioavailability and Food Effect of Solid Oral Formulation and Optional Open-Label, Non Randomized Study to Evaluate Metabolism and Excretion of PF 07817883 and Optional Randomized, Open-Label Study to Assess the Effect of PF 07817883 on Pharmacokinetics of Midazolam in Healthy Adult Participants.

Brief Title:

A Multipart Phase 1 Study Including Single Ascending Dose, Multiple Ascending Dose, Relative Bioavailability, Food Effect, Metabolism and Excretion and Drug-Drug Interaction of PF-07817883 in Healthy Adult Participants.

Regulatory Agency Identification Number(s):

US IND Number:	162644
EudraCT Number:	2022-002871-12
ClinicalTrials.gov ID:	NCT05580003
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5091001
Phase:	Phase 1

Rationale:

The current study is the FIH study of PF-07817883 in healthy adult participants. It is a 6-part study combining PART-1: SAD, PART-2: MAD, PART-3: RBA/FE PART-4: ME, PART-5: DDI, and PART-6: SE. PART-1 and PART-2 will evaluate safety, tolerability, and PK of single and multiple escalating oral doses of PF-07817883 in healthy adult participants, respectively. PART-2 of the study may also evaluate the safety, tolerability, and PK in Japanese and Chinese participants. PART-3 will evaluate RBA and FE of up to 2 new PF-07817883 oral formulations. PART-4 will evaluate the ME of PF-07817883. PART-5 will evaluate the effect of steady-state PF-07817883 on PK of midazolam in healthy participants. PART-6 will assess the safety, tolerability, and PK of PF-07817883 at SE.

Results from this study will inform the study design of the Phase 2/3 studies in COVID-19 patients.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Objectives and Endpoints:

PART-1: SAD

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability following single ascending doses of PF-07817883.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.
Secondary:	**Secondary:**

• To assess the plasma PK profile of PF-07817883 following single ascending doses of PF-07817883.	• Plasma PK parameters of PF-07817883:
	  • C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn).
	  • If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.

PART-2: MAD

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability following multiple ascending doses of PF-07817883.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.
Secondary:	**Secondary:**

• To assess the plasma PK profile of PF-07817883 on Days 1, 5 and 10 following multiple ascending doses of PF-07817883.	• Plasma PK parameters of PF-07817883:
	  • C_{max}, T_{max}, AUC_{tau}, C_{12}, C_{max}(dn), AUC_{tau}(dn), C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR,CL/F and V_z/F.
	  • If data permit, $t_{½}$.

• To assess the renal excretion of PF-07817883 on Day 10 following multiple ascending doses of PF-07817883.	• PF-07817883 urinary PK parameters: • Ae_{tau} and Ae_{tau}%, CL_r.

PART-3: RBA/FE

Objectives	Endpoints
Primary:	**Primary:**
• To determine the oral bioavailability of oral formulation(s) of PF-07817883 relative to suspension.	• The ratio of AUC_{last}, AUC_{inf} and C_{max} of oral formulation(s) and suspension.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Objectives	Endpoints
Secondary:	**Secondary:**
• To evaluate the effect of food (high-fat high-calorie meal) on the exposure of PF-07817883 following a single oral dose of PF-07817883 tablet formulation(s).	• The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation under fed condition and fasted condition.
• To determine the PK of PF-07817883 following oral administration of tablet formulation(s) and suspension of PF-07817883.	• Plasma PK parameters of PF-07817883: T_{max}, C_{max}, AUC_{last}, if data permit AUC_{inf}, $t_{½}$, CL/F, V_z/F.
• To determine the safety and tolerability of PF-07817883 following oral administration of tablet formulation(s) and suspension of PF-07817883.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.

PART-4: ME

Objectives	Endpoints
Primary:	**Primary:**
• To determine the extent of excretion of drug-related material in urine and feces after a single oral administration of PF-07817883.	• Total recovery of drug-related material in urine and feces separately, and both routes combined, expressed as a percent of total dose administered.
Secondary:	**Secondary:**
• To determine the PK of PF-07817883 following a single oral administration of PF-07817883.	• Plasma PK parameters of PF-07817883: T_{max}, C_{max}, AUC_{last}, if data permit AUC_{inf}, $t_{½}$, CL/F, V_z/F.
• To determine the safety and tolerability of PF-07817883 after a single oral administration of PF-07817883.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.

PART-5: DDI

Objectives	Endpoints
Primary Objective:	**Primary Endpoint:**
• To estimate the effect of PF-07817883 on the PK of midazolam.	• Midazolam plasma PK parameters: C_{max} and AUC_{inf} (if data permit, otherwise AUC_{last}) with PF-07817883 (test) versus without PF-07817883 (reference).

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Objectives	Endpoints
Secondary Objective:	**Secondary Endpoints:**
• To evaluate the safety and tolerability of PF-07817883 in healthy participants in the absence and presence of midazolam. • To evaluate the effects of PF-07817883 on additional PK parameters of midazolam in healthy participants.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs. • Midazolam plasma PK parameters: T_{max}, AUC_{last}, and if data permit $t_{½}$, CL/F, and V_z/F for midazolam with and without coadministration of PF-07817883.

PART-6: SE cohort

Objectives	Endpoints
Primary Objective:	**Primary Endpoint:**
• To assess the safety and tolerability of a SE of PF-07817883 administered as split dosing.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.
Secondary Objective:	**Secondary Endpoints:**

• To assess the plasma PK of PF-07817883 at a SE of PF-07817883 administered as split dosing.	• Plasma PK parameters of PF-07321332:
	  • C_{max}, T_{max}, AUC_{last}
	  • If data permit, AUC_{inf}, $t_{½}$.

Overall Design:

This 6-part, Phase 1, FIH study will combine PART-1: SAD, PART-2: MAD, including Japanese and Chinese cohorts, PART-3: RBA/FE cohort, PART-4: ME cohort, PART-5: DDI cohort, and PART-6: SE cohort.

PART-1 and PART-2 are a randomized, double-blind, sponsor-open, placebo-controlled trial to evaluate safety, tolerability, and PK of single and multiple escalating oral doses of PF-07817883 in healthy adult participants, respectively. PART-2 of the study may also evaluate the safety, tolerability, and PK in Japanese and Chinese participants. PART-3 is a randomized, open-label, cross-over, study to evaluate RBA and FE of up to 2 new PF-07817883 oral formulations. PART-4 is an open-label, non-randomized, single period cohort to evaluate the ME of PF-07817883. PART-5 is an open-label, randomized, cross-over cohort to evaluate the effect of steady-state PF-07817883 on PK of midazolam in healthy participants. PART-6 is a sponsor-open, randomized, 3-treatment, 3-period, 6-sequence, cross-over, placebo-and positive-controlled study to evaluate safety, tolerability, and PK of PF-07817883 at SE.

PART-1: SAD

SAD will include 2 interleaving cohorts with a total of approximately 16 participants planned (approximately 8 participants in each cohort [6 active: 2 placebo]), with 3-period, cross-over in each cohort. Period 3 is an optional period which may be used to further explore PK at

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

additional doses or assess FE (high-fat high-calorie meal), based on emerging safety, tolerability, and PK assessments.

There will be a washout interval of ≥5 days between dosing to a given participant. Participants will be required to stay at the CRU for the duration of the washout interval. However, they may be released at the discretion of the investigator. The washout interval may be adjusted based on data emerging from previous cohorts/periods.

PART-2: MAD

The proposed MAD study design will be parallel cohorts, with 10 days of dosing. PART-2 will consist of approximately 2 to 6 cohorts, including up to 4 optional cohorts (Cohorts 5, 6, 7, and 8) with approximately 6 participants in each cohort (4 active: 2 placebo). Cohorts 7 and 8 are optional Japanese and Chinese participants cohort, respectively.

PART-3: RBA/FE

This cohort will be an open-label, randomized, 4-period, 6-sequence cross-over SD cohort evaluating the RBA of 2 new PF-07817883 oral formulation(s) compared to PF-07817883 oral suspension and to evaluate the effect of food on the bioavailability of the PF-07817883 oral formulation(s) in healthy adult participants. Approximately 12 participants may be enrolled in PART-3 of the study with approximately equal number of participants randomized to each sequence. In this part, there will be a washout interval of at least 3 days between dosing to a given participant in each period.

PART-4: ME

This part will include a single cohort of approximately 6 male participants. The dose of this cohort will be decided based on the emerging PK and safety data and the selected dose will be less than or equal to a dose deemed safe and tolerable in PART-1. Each participant will receive a single dose of PF-07817883 at 0 hr on Day 1 after at least 10 hr of fasting. The participants will be discharged on Day 11.

PART-5: DDI

This part may consist of up to 2 cohorts (Cohort 11 and optional Cohort 12). Each cohort consists of 2 treatments, 2 sequences, and 2 periods with a cross-over design to evaluate the effect of steady-state PF-07817883 on the PK of midazolam in healthy adult participants. The dose of PF-07817883 in Cohort 11 is 600 mg BID and the dose of Cohort 12 will be decided based on the emerging PK data from Cohort 11. This part will consist of 2 treatments: single oral dose of 5 mg midazolam alone (Treatment A) and multiple oral doses of PF-07817883 in combination with a single oral dose of 5 mg midazolam (Treatment B). Each enrolled participant will be randomly assigned to 1 of 2 sequences to receive 2 treatments in 2 periods. In each cohort, a total of approximately 14 healthy participants will be enrolled to ensure at least 12 participants will complete this part.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

PART-6: SE

This cohort will include approximately 24 adult healthy participants randomized to 3-period, 6-sequence, cross-over design to explore safety, tolerability, and PK at SE. The participants randomized to treatment will receive 6000 mg as 2 split doses of PF-07817883 3000 mg administered at 0 and 1 h. The participant randomized to placebo will receive placebo at 0 and 1h. The participants randomized to moxifloxacin will receive moxifloxacin 400 mg and placebo at 0 and 1h, respectively. Sentinel dosing will be implemented in this cohort. Treatment assignments to PF-07817883 and placebo will be blinded to the participants, investigator and CRU staff (except pharmacy staff) but open to the sponsor. Administration of moxifloxacin and placebo in participants randomized to moxifloxacin treatment will be open label.

Number of Participants:

A total of up to 122 participants (16 in PART-1: SAD, up to 36 [with 2 cohorts and 4 optional cohorts] in PART-2: MAD, 12 in PART-3: RBA/FE cohort, 6 in PART-4: ME, up to 28 [with 2 cohorts of 14 each] in PART-5: DDI and 24 in PART-6: SE) are planned to be enrolled in this study.

Note: "Enrolled" means a participant's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

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:

Age and Sex:

1. Participants, male or female, 18 to 60 years of age, inclusive, at the time of signing the ICD. Only Male participants will be included in PART-4.

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, PE, laboratory tests, and standard 12-lead ECG.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Other Inclusion Criteria:

3. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb). A body weight of 45 kg may be considered in selected cases.

4. For optional Japanese/Chinese cohorts or PART-5 only: Japanese participants who have 4 Japanese biologic grandparents who were born in Japan. Chinese participants who were born in mainland China and both parents are of the Chinese descent.

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

Exclusion Criteria

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

Medical Conditions:

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

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic 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 28 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention.

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 halflives preceding the first dose of study intervention used in this study (whichever is longer).

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Diagnostic Assessments:

7. A positive urine drug test.

8. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest.

9. Renal impairment as defined by an eGFR in adults, of <75 mL/min.

10. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results.

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.

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

13. Use of tobacco or nicotine-containing products in excess of the equivalents of 5 cigarettes per day or 2 chews of tobacco per day.

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. Pregnant or breastfeeding women.

16. **PART-6 Only:** Participants who according to the product label for moxifloxacin, would be at increased risk if dosed with moxifloxacin (ie, including but not limited to participants with history of myasthenia gravis, tendinitis/tendon rupture).

17. **PART-6 Only:** History of hypersensitivity, allergy, severe adverse drug reaction or intolerance to quinolone antibiotics, including moxifloxacin.

Study Arms and Duration:

Study Intervention(s)				
Intervention Name	PF-07817883	Placebo	Midazolam	Moxifloxacin
Arm Name (group of participants receiving a specific treatment or no treatment)	PART-1 through PART-5	PART-1 and PART-2.	PART-5.	PART-6

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Study Intervention(s)				
Type	Drug	Drug	Drug	Drug
Dose Formulation	Suspension/Solution or solid oral formulation (eg, tablet)	Suspension/Solution or solid oral formulation (eg, tablet)	Solution.	Tablet
Unit Dose Strength(s)	Planned oral suspension/solution doses ranging from 150 mg to 6000 mg. Planned nominal solid oral formulation strength 100-400 mg pending final formulation development and dose.	0 mg	As available locally.	As available locally.
Dosage Level(s)	Planned oral suspension/solution doses ranging from 150 mg to 6000 mg. Planned nominal solid oral formulation strength 100 - 400 mg pending final formulation development and dose.	0 mg	5 mg SD	400 mg
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Probe substrate	Active control
IMP or NIMP/AxMP	IMP	IMP	NIMP	NIMP/AxMP
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.	Provided locally by the CRU.	Provided locally by the CRU.
Packaging and Labeling	Materials (API and components) for extemporaneous prep of oral suspensions will be provided in bulk. Tablets will be provided in bulk. CRU staff will prepare individual doses for administration. Individual dose containers will be labeled by site staff per country requirement.	Materials (API and components) for extemporaneous prep of oral suspensions will be provided in bulk. Solid oral formulation will be provided in bulk. CRU staff will prepare individual doses for administration. Individual dose containers will be labeled by site staff per country requirement.	CRU will procure commercially labeled materials.	CRU will procure commercially labeled materials.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Study Intervention(s)				
Current/Former Name(s) or Alias(es)	PF-07817883	Placebo	As available locally.	As available locally.

Statistical Methods:

The sample size for PART-1 and PART-2 of the study has been chosen based on the need to minimize exposure of healthy participants to a new chemical entity and the requirements to provide adequate safety and toleration and PK information at each dose level.

For PART-3, a sample size of 12 participants will provide adequate precision to compare the RBA of up to 2 new oral formulation(s) of PF-07817883 relative to oral suspension.

For PART-4: A sample size of approximately 6 male participants (with at least 4 completers) is chosen based on the industry standard sample size for ME studies. This sample size was not justified by any empirical data or hypothesis testing criteria.

For PART-5: A sample size of 14 participants (with at least 12 completers) is chosen based on the need to provide sufficient precision to detect a 1.25-fold difference in Midazolam AUC_{inf}.

For PART-6: A sample size of approximately 24 participants will provide at least 87% power to demonstrate assay sensitivity for C-QTc modeling with pre-dose baseline as reported in Huang et al (2021).

The data from the 6 parts of this study will be analyzed and reported separately in a single CSR. Exploratory analyses may not be included within the CSR.

All safety analyses will be performed on the safety analysis set, which is defined as all participants randomly assigned to study intervention and who receive at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

For each part separately, plasma concentrations will be listed and summarized descriptively by PK sampling time and treatment. The plasma PK parameters and urine PK parameters (PART-2 only) of PF-07817883 and midazolam (PART-5 only), as applicable, will be summarized descriptively by treatment. No formal inferential statistics will be applied to the plasma PK data apart from the comparisons of new oral formulation(s) and FE in either PART-1 or PART-3 and the estimation of the effect of PF-07817883 on the PK of midazolam in PART-5.

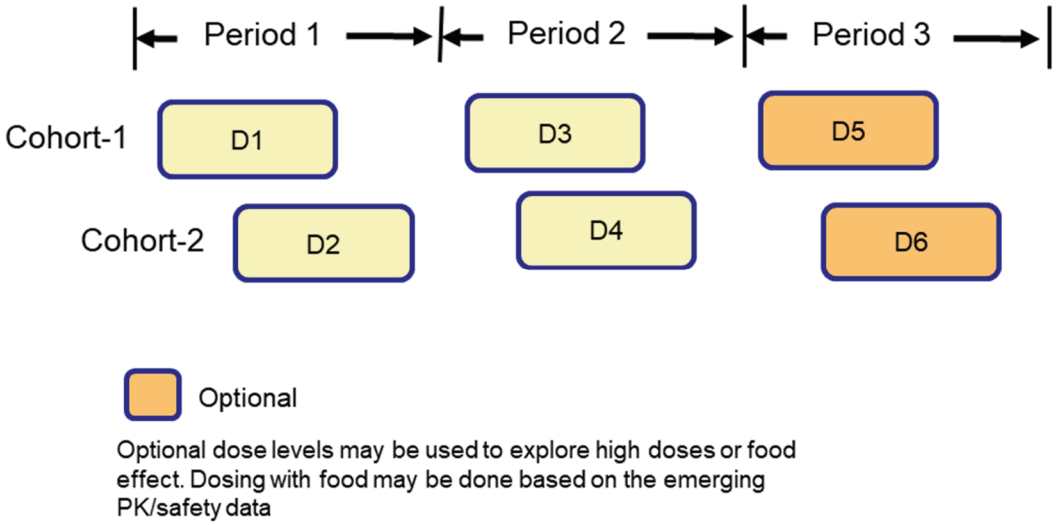
Ethical Considerations:

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1.2. Schema

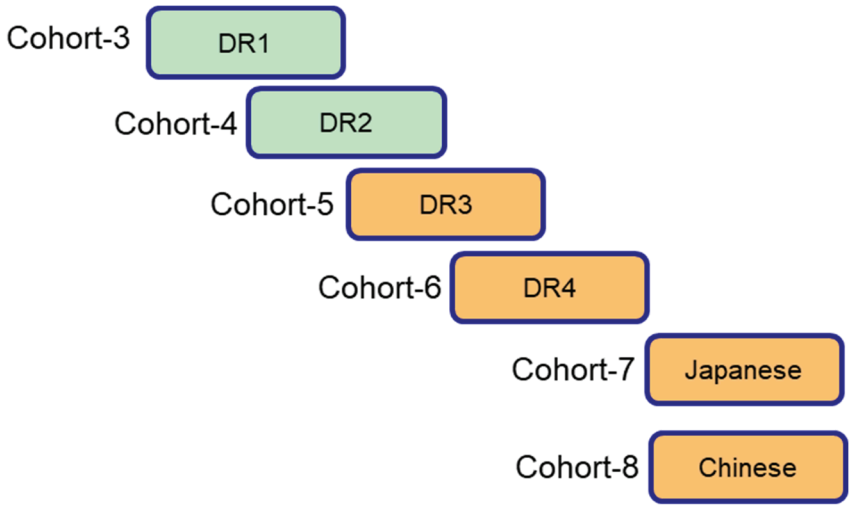
1.2.1. PART-1: SAD



SAD dose levels D1 to D6 in Table 15 in Section 4.3.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1.2.2. PART-2: MAD

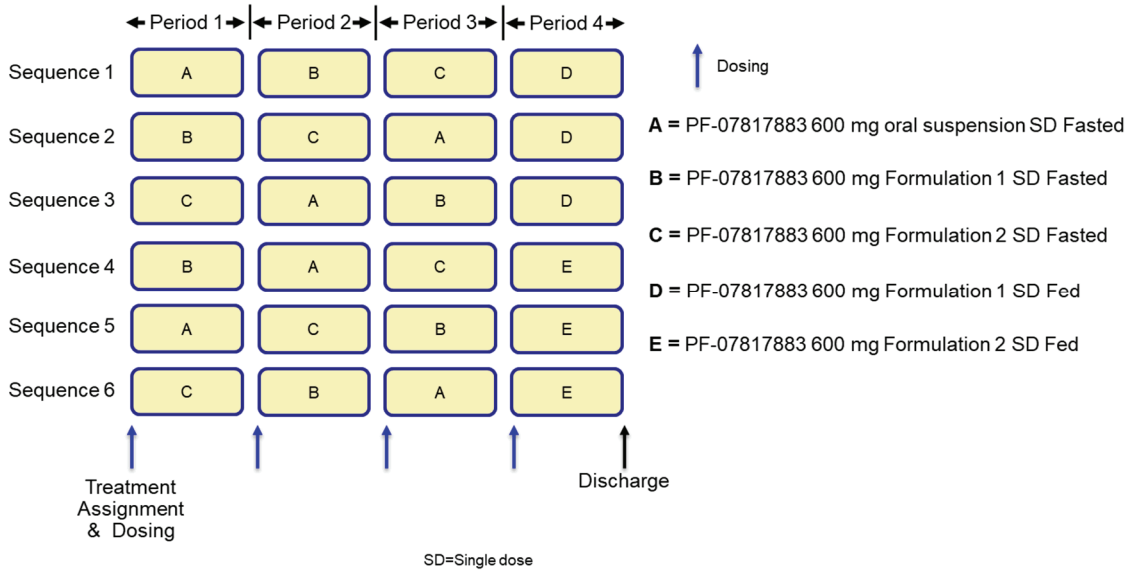


MAD dosing regimens DR1 to DR4 are listed in Table 16 in Section 4.3.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1.2.3. PART-3: RBA/FE

Cohort-9



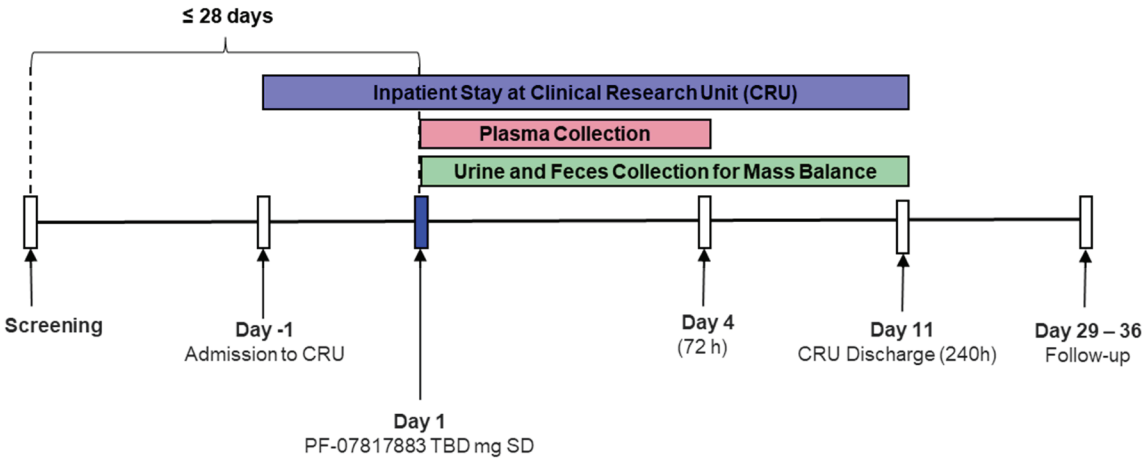
Formulation 1: CCI [redacted]

Formulation 2: CCI [redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1.2.4. PART-4: ME

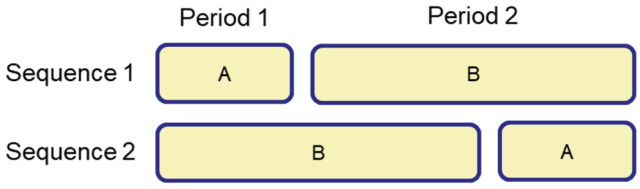
Cohort 10



TBD: To be decided; SD=Single dose

1.2.5. PART-5: DDI

Cohort 11

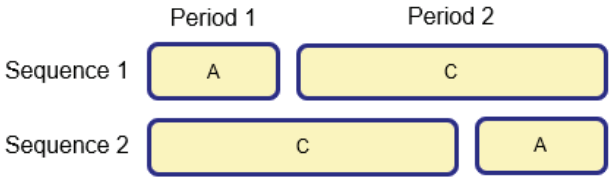


A = Treatment A: Midazolam 5 mg SD with 2-day washout

B = Treatment B: PF-07817883 TBD mg BID for 10 days +Midazolam 5 mg SD on Day 10 with 7-day washout

TBD: To be decided; SD=Single dose; BID=two times a day

Cohort-12 (Optional)



A = Treatment A: Midazolam 5 mg SD with 2-day washout

C = Treatment C: PF-07817883 TBD mg BID for 10 days +Midazolam 5 mg SD (AM dose) on Day 5 and Day 10 (AM dose) with 7-day washout

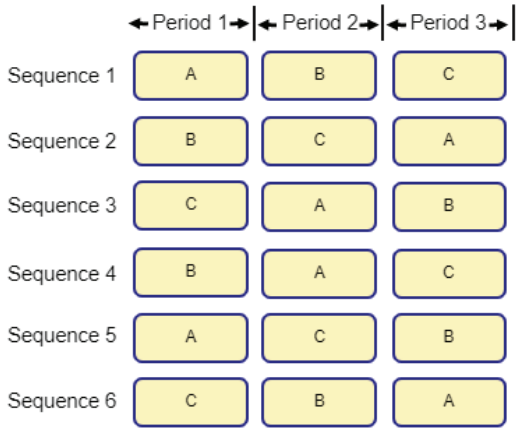
TBD: To be decided; SD=Single dose; BID=two times a day

Washout duration may be modified based on emerging data.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1.2.6. PART-6: SE

Cohort-13



A = Treatment A: PF-07817883 6000 mg, [2 divided doses (3000 mg) to be administered at 0 and 1h], Oral suspension, SD, Fasted

B = Placebo

C = Moxifloxacin 400 mg, SD

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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.

1.3.1. PART-1: SAD

Table 1. PART-1: SAD Cohorts

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Periods 1-3**																	**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**											**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Days 29-36**		• Follow-up to occur 28-35 days after administration of last dose of study intervention via telephone contact.
Hours After Dose			**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**	**72h**	**96h**	**120h**			
Informed consent	X																				
Inclusion/exclusion criteria	X	X																			• Not required in Period 2 and Period 3.
Demographics (including height & weight)	X																				• Refer to Section 8.1.1.2.
Medical/Medicine history	X	X																			• Only required in Periods 2 and 3 if discharged from the site.
SARS-CoV-2 RT-PCR		X																			• Only required in Periods 2 and 3 if discharged from the site. • As per local CRU procedures.
COVID-19 signs and symptoms	X	X																			• As per local CRU procedures.
CRU Confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X				• Participants remain confined until Day 5 in last period.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 1. PART-1: SAD Cohorts

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Periods 1-3**																**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**											**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Days 29-36**		• Follow-up to occur 28-35 days after administration of last dose of study intervention via telephone contact.
Hours After Dose			**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**	**72h**	**96h**	**120h**			
PE	X	X						X									X			X	• Full PE may be performed at Screening or admission in Period 1 only. Further full/limited PE at PI's discretion. • Limited PE targeted to neuro-muscular exam to be done prior to dosing and post-dose on Day 1, 2(±0.5) h and ~96h post-dosing.
Vital signs (respiratory rate, PR, BP)	X		X		X	X	X	X	X	X	X	X		X						X	• Refer to Section 8.3.2.
12-Lead ECG (triplicate)	X		X		X	X	X	X	X	X	X	X		X						X	• Singlet at screening. • Pre-dose (0h) on Day 1 triplicate measurement to be collected at approximately -1h, -0.5h and 0h per local procedure.
Continuous cardiac telemetry monitoring			X	→	→	→	→	→	→	→	X										• Baseline telemetry to be recorded for at least 2 hours between admission and prior to dosing in Period 1 only while awake (Section 8.3.3.1).
Contraception check	X	X															X		X	X	• Day 5 in last period only if not discharged.
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
Study intervention administration																					
PF-07817883 or Placebo			X																		

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 1. PART-1: SAD Cohorts

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Periods 1-3																F/U Contact	E/T	Notes
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**											**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Days 29-36**		• Follow-up to occur 28-35 days after administration of last dose of study intervention via telephone contact.
Hours After Dose			**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**	**72h**	**96h**	**120h**			
Blood Samples for:																				
Pregnancy test (WOCBP only)	X	X															X			X	• Day 5 in last period only if not discharged.
Safety laboratory (≥4h fasting)	X	X												X	X		X			X	• Day -1 performed in Periods 2 and 3 only if discharged from CRU.
HIV, HBsAg, HBcAb and HCVAb	X																				
Serum FSH (post-menopausal females only)	X																				
Retained Research Samples for Genetics (Prep D1)			X																		• Only in Period 1. • If not collected on the designated collection day, collect at the next available time point.
Plasma PK (PF-07817883)			X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	
Drug-related material measurement and metabolic profiling			X			X			X			X		X							• Only for selected dose levels. The dose level to be decided based on emerging data.
Urine Samples for:																				
Drug screen testing	X	X																			• Not required in Period 2 or Period 3 if the participants were not discharged.
Urinalysis	X	X												X	X		X			X	
Drug-related material measurement and metabolic profiling		X	X	→	→	→	→	→	→	→	→	→	→	X	X	X	X	X			• Only for selected dose levels. The dose level to be decided based on emerging data. • Collected in 24 h intervals. • Pre-dose 'blank' to be collected (Section 8.5.5).

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 1. PART-1: SAD Cohorts

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Periods 1-3**																	**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**											**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Days 29-36**		• Follow-up to occur 28-35 days after administration of last dose of study intervention via telephone contact.
Hours After Dose			**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**	**72h**	**96h**	**120h**			
Feces Collection for:																					
Drug-related material measurement and metabolic profiling		X	X	→	→	→	→	→	→	→	→	→	→	X	X	X	X	X			• Only for selected dose levels. The dose level to be decided based on emerging data. • Collected in 24 h intervals. • Pre-dose 'blank' to be collected (Section 8.5.5).

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1.3.2. PART-2: MAD

Table 2. PART-2: MAD Cohorts (Including Optional Japanese and Chinese Cohorts)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**														**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Days 38-45**		• Days 1, 5, and 10: Refer to Table 3.
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Demographics (including height & weight)	X																• Refer to Section 8.1.1.2.
Medical/Medicine history	X	X															
SARS-CoV-2 RT-PCR		X															• As per local CRU procedures.
COVID-19 signs and symptoms	X	X															• As per local CRU procedures.
CRU Confinement		X	→	→	→	→	→	→	→	→	→	→	→	X			
PE	X	X					X							X		X	• Full PE may be performed at Screening or admission. Further full/limited PE at PI's discretion. • Limited PE targeted to neuro-muscular exam to be done on Day 5, 2(±0.5) h and Day 12.
Vital signs (respiratory rate, PR, BP)	X		X	X			X			X		X		X		X	• Pre-dose on the dosing days. • Refer to Section 8.3.2.
12-Lead ECG (triplicate)	X		X	X			X			X		X		X		X	• Singlet at screening. • Pre-dose on the dosing days. • Pre-dose on Day 1, triplicate measurement at baseline to be collected at approximately -1h, -0.5h

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 2. PART-2: MAD Cohorts (Including Optional Japanese and Chinese Cohorts)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**														**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Days 38-45**		• Days 1, 5, and 10: Refer to Table 3.
																	and 0h per local procedure.
Contraception check	X	X												X	X	X	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
Study intervention administration																	
PF-07817883 or Placebo (BID)			X	X	X	X	X	X	X	X	X	X					• On Day 10, morning dose only.
Blood samples for:																	
Pregnancy test (WOCBP only)	X	X												X		X	
Safety laboratory (≥4h fasting)	X	X		X			X			X		X		X		X	
HIV, HBsAg, HBcAb and HCVAb	X																
Serum FSH (post-menopausal females only)	X																
Retained Research Samples for Genetics (Prep D1)			X														• If not collected on the designated collection day, collect at the next available time point.
Plasma PK (PF-07817883)			X	X	X		X	X		X		X	X	X		X	
PK Biomarkers			X									X	X				
Optional PK microsampling (Tasso®) for PF-07817883							X	X		X							• NH CRU only. • Pre-dose only on Days 6 and 8.
Optional Blood/plasma ratio sample							X	X		X							• NH CRU only. • Pre-dose only on Days 6 and 8.
Urine samples for:																	
Drug screen testing	X	X															
Urinalysis	X	X		X			X			X		X		X		X	
PK			X									X					

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 3. PART-2: PK Days (Day 1, Day 5, Day 10) in MAD Cohorts (Including Optional Japanese and Chinese Cohorts)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Treatment Period on PK Days**																												**Notes**
Days Relative to Day 1	**Day 1**										**Day 5**										**Day 10**									
Planned Hours Post 1st Dose on that day	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	
PE															X																• Limited PE targeted to neuro-muscular exam to be done at post-dose on Day 5, 2(±0.5) h.
Vital signs (respiratory rate, PR, BP)	X										X		X		X						X		X		X					• Refer to Section 8.3.2.
12-Lead ECG (Triplicate)	X										X		X		X						X		X		X					• Pre-dose on Day 1, triplicate measurement at baseline to be collected at approximately -1h, -0.5h and 0h per local procedure.
Study intervention administration																															
PF-07817883 or Placebo (BID dosing)	X								X		X								X		X										
Blood samples for:																															
Safety laboratory (≥4h fasting)											X										X										
Retained Research Samples for Genetics (Prep D1)	X																														
PK Biomarker	X																				X		X		X			X			
Plasma PK (PF-07817883)	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	
Optional PK microsampling (Tasso®) for PF-07817883														X																	
Blood/plasma ratio sample														X																	
Urine samples for:																															
Urinalysis											X										X										
PK and metabolic profiling (BID dosing)	X																				X	→	→	→	→	→	→	→	X		

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1.3.3. PART-3: RBA/FE

Table 4. PART-3: RBA/FE Cohort

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Periods 1-4**													**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1 in each period	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Days 29-36**		• Day 3 only in last period if not discharged. • F/U only in last period.
Planned Hours Post-Dose			**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**			
Informed consent	X																
Inclusion/exclusion criteria	X	X															• Period 1 only.
Demographics (including height & weight)	X																• Refer to Section 8.1.1.2.
Medical/Medicine history	X	X															• Only if discharged from the site in Periods 2-4.
SARS-CoV-2 RT-PCR		X															• Not required in Periods 2-4 if the participants were not discharged. • As per local CRU procedures.
COVID-19 signs and symptoms	X	X															• Not required in Periods 2-4 if the participants were not discharged. • As per local CRU procedures.
CRU Confinement		X	→	→	→	→	→	→	→	→	→	→	→	X			
PE	X	X														X	• PE may be performed at Screening or admission.
Vital signs (respiratory rate, PR, BP)	X		X											X		X	• Refer to Section 8.3.2.
12-Lead ECG (single)	X		X											X		X	• Day 3 only in last period.
Contraception check	X	X												X	X	X	• Day -1 not required in Periods 2 - 4 if the participants were not discharged. • Day 3 performed only at discharge from the CRU.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 4. PART-3: RBA/FE Cohort

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Periods 1-4**													**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1 in each period	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Days 29-36**		• Day 3 only in last period if not discharged. • F/U only in last period.
Planned Hours Post-Dose			**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**			
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
Study intervention administration																	
PF-07817883			X														
Blood Samples for:																	
Pregnancy test (WOCBP only)	X	X												X		X	• Day -1 not required in Periods 2 - 4 if the participants were not discharged. • Day 3 performed only at discharge from the CRU.
Safety laboratory (≥4h fasting)	X	X												X		X	• Day 3 in last Period only
HIV, HBsAg, HBcAb and HCVAb	X																
Serum FSH (post-menopausal females only)	X																
Retained Research Samples for Genetics (Prep D1)			X														• Period 1 only. • If not collected on the designated collection day, collect at the next available time point.
Plasma PK (PF-07817883)			X	X	X	X	X	X	X	X	X	X	X	X		X	
Urine samples for:																	
Drug screen testing	X	X															• Not required in Period 2 or Period 3 or Period 4 if the participants were not discharged.
Urinalysis	X	X												X		X	• Day 3 in last Period only

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 4. PART-3: RBA/FE Cohort

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Periods 1-4**													**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1 in each period	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Days 29-36**		• Day 3 only in last period if not discharged. • F/U only in last period.
Planned Hours Post-Dose			**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**			
Other Assessments																	
Taste Assessment			X		X		X	X		X							• For suspension, only assessed immediately following dosing (within 1 min), 5 min, 10 min and 20 minutes of administration. • For solid oral formulations, 0h assessment will be done within 5 min of administration.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1.3.4. PART-4: ME

Table 5. PART-4: ME Cohort

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**																**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Day 4**	**Day 5-10**	**Day 11**	**Days 29-36**		
Planned Hours Post-Dose			**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**	**72h**	**96h-216h**	**240h**			
Informed consent	X																			
Inclusion/exclusion criteria	X	X																		
Demographics (including height & weight)	X																			• Refer to Section 8.1.1.2.
Medical/Medicine history	X	X																		
SARS-CoV-2 RT-PCR		X																		• As per local CRU procedures.
COVID-19 signs and symptoms	X	X																		• As per local CRU procedures.
CRU Confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X			• May be admitted earlier to facilitate collection of pre-dose fecal sample.
PE	X	X																	X	• PE may be performed at Screening or admission.
Vital signs (respiratory rate, PR, BP)	X		X														X		X	• Refer to Section 8.3.2.
12-Lead ECG (Single)	X		X														X		X	
Contraception check	X	X															X	X	X	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
Study intervention administration																				
PF-07817883			X																	
Blood Samples for:																				
Safety laboratory (≥4h fasting)	X	X															X		X	
HIV, HBsAg, HBcAb and HCVAb	X																			
Retained Research Samples for Genetics (Prep D1)			X																	• If not collected on the designated collection day, collect at the next available time point.
Plasma PK (PF-07817883)			X	X	X	X	X	X	X	X	X	X	X	X	X				X	

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 5. PART-4: ME Cohort

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**																	**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Day 4**	**Day 5-10**	**Day 11**	**Days 29-36**		
Planned Hours Post-Dose			**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**	**72h**	**96h-216h**	**240h**			
Drug-related material measurement and metabolite profiling			X		X	X	X	X		X	X		X							
Urine Samples for:																				
Drug screen testing	X	X																		
Urinalysis	X	X															X		X	
Drug-related material measurement and metabolic profiling			X	→	→	→	→	→	→	→	→	→	X	X	X	X	X			• Collected in 24 h intervals post-dose. • Pre-dose 'blank' to be collected (Section 8.5.5).
Feces Collection for:																				
Drug-related material measurement and metabolic profiling			X	→	→	→	→	→	→	→	→	→	X	X	X	X	X			• Collected in 24 h intervals post-dose. • Pre-dose 'blank' to be collected (Section 8.5.5).

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1.3.5. PART-5: DDI

Table 6. PART-5: DDI for Sequence 1

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**		**Treatment A**												**Treatment B or Treatment C**												**F/U**	**E/T**	**Notes**
	Period 1														**Period 2**														
Days relative to Day 1 in each Period	**-28 to -2**	**-1**	**1**										**2**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**38 - 45**		• Days 1, 5, and 10 in Period 2: Refer to Table 8.
Hours After Dose			0	0.5	1	1.5	2	4	6	8	12	16	24	36															
Informed consent	X																												
Inclusion/exclusion criteria	X	X																											
Demographics (including height & weight)	X																											• Refer to Section 8.1.1.2.	
Medical/Medicine history	X	X																											
SARS-CoV-2 RT-PCR		X																										• As per local CRU procedures.	
COVID-19 signs and symptoms	X	X																										• As per local CRU procedures.	
CRU Confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X			
PE	X	X																										X	• PE may be performed at Screening or admission.
Vital signs (respiratory rate, PR, BP)	X		X		X		X								X	X			X			X		X		X		X	• Refer to Section 8.3.2.
12-Lead ECG (Single)	X		X				X								X	X			X			X		X		X		X	

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 6. PART-5: DDI for Sequence 1

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**		**Treatment A**												**Treatment B or Treatment C**												**F/U**	**E/T**	**Notes**
	Period 1														**Period 2**														
Days relative to Day 1 in each Period	**-28 to -2**	**-1**	**1**										**2**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**38 - 45**		• Days 1, 5, and 10 in Period 2: Refer to Table 8.
Hours After Dose			0	0.5	1	1.5	2	4	6	8	12	16	24	36															
Contraception check	X	X																								X	X	X	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
Study intervention administration																													
PF-07817883 (BID)															X	X	X	X	X	X	X	X	X	X					• Only Morning dose on Day 10 in Period 2.
Midazolam			X																X					X					• Period 2, Day 5 midazolam dose in optional Cohort 12 only.
Blood samples for:																													
Pregnancy test (WOCBP only)	X	X																								X			
Safety laboratory (≥4h fasting)	X	X													X				X					X		X			
HIV, HBsAg, HBcAb and HCVAb	X																												
Serum FSH (post-menopausal females only)	X																												

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 6. PART-5: DDI for Sequence 1

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**		**Treatment A**											**Treatment B or Treatment C**												**F/U**	**E/T**	**Notes**
	Period 1													**Period 2**														
Days relative to Day 1 in each Period	**-28 to -2**	**-1**	**1**										**2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**38 - 45**		• Days 1, 5, and 10 in Period 2: Refer to Table 8.
Hours After Dose			0	0.5	1	1.5	2	4	6	8	12	16	24	36														
Retained Research Samples for Genetics (Prep D1)			X																									• If not collected on the designated collection day, collect at the next available time point.
Plasma PK (PF-07817883)															X	X	X		X	X		X		X	X	X			
Midazolam			X	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X			X	X	X			• In Period 2, Day 11 at 24 and 36h and Day 12 at 48h post-dose. • Period 2, Day 1 (pre-dose) sample is 48h post-dose sample of Period 1. • In Period 2, Days 5, 6 and 7 PK samples is optional Cohort 12 only.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 6. PART-5: DDI for Sequence 1

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**		**Treatment A**												**Treatment B or Treatment C**												**F/U**	**E/T**	**Notes**
	Period 1														**Period 2**														
Days relative to Day 1 in each Period	**-28 to -2**	**-1**	**1**										**2**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**38 - 45**		• Days 1, 5, and 10 in Period 2: Refer to Table 8.
Hours After Dose			0	0.5	1	1.5	2	4	6	8	12	16	24	36															
Urine samples for:																													
Drug screen testing	X	X																											
Urinalysis	X	X													X				X					X		X			

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 7. PART-5: DDI for Sequence 2

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening		Treatment B or Treatment C										Wash-Out			Treatment A															F/U	E/T	Notes
	Period 1															Period 2																	
Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13-17	1											2		3	29-36		• Day 1, Day 5 and Day 10 in Period 1: Refer to Table 8.
Hours After Dose																0	0.5	1	1.5	2	4	6	8	12	16	24	36	48			
Informed consent	X																															
Inclusion/exclusion criteria	X	X																														
Demographics (including height & weight)	X																														• Refer to Section 8.1.1.2.
Medical/Medicine history	X	X																														
SARS-CoV-2 RT-PCR		X																													• As per local CRU procedures.
COVID-19 signs and symptoms	X	X																													• As per local CRU procedures.
CRU Confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X			
PE	X	X																													X	• PE may be performed at Screening or admission.
Vital signs (respiratory rate, PR, BP)	X		X	X			X			X		X		X		X		X		X									X		X	• Refer to Section 8.3.2.
12-Lead ECG	X		X	X			X			X		X		X		X				X									X		X	

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 7. PART-5: DDI for Sequence 2

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**		**Treatment B or Treatment C**										**Wash-Out**			**Treatment A**															**F/U**	**E/T**	**Notes**
	Period 1															**Period 2**																	
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13-17**	**1**											**2**		**3**	**29-36**			• Day 1, Day 5 and Day 10 in Period 1: Refer to Table 8.
Hours After Dose																0	0.5	1	1.5	2	4	6	8	12	16	24	36	48				
Contraception check	X	X																										X	X	X	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
Study intervention administration																															
PF-07817883 (BID)			X	X	X	X	X	X	X	X	X	X																			• Only Morning dose on Day 10 in Period 1.
Midazolam							X					X				X															• Period 1, Day 5 midazolam dose in optional Cohort 12 only.
Blood samples for:																															
Pregnancy test (WOCBP only)	X	X																										X			
Safety laboratory (≥4h fasting)	X	X					X					X		X		X												X			
HIV, HBsAg, HBcAb and HCVAb	X																														

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 7. PART-5: DDI for Sequence 2

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**		**Treatment B or Treatment C**										**Wash-Out**			**Treatment A**															**F/U**	**E/T**	**Notes**
	Period 1															**Period 2**																	
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13-17**	**1**										**2**		**3**	**29-36**			• Day 1, Day 5 and Day 10 in Period 1: Refer to Table 8.
Hours After Dose																0	0.5	1	1.5	2	4	6	8	12	16	24	36	48				
Serum FSH (post-menopausal females only)	X																														
Retained Research Sample for Genetics (Prep D1)			X																												
Plasma PK (PF-07817883)			X	X	X		X	X		X		X	X	X																	
Midazolam							X	X	X			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			• In Period 1, Day 11 at 24 and 36 h and Day 12 at 48 h post-dose. • In Period 1, Days 5, 6 and 7 PK samples in optional Cohort 12 only.
Urine samples for:																															
Drug screen testing	X	X																													
Urinalysis	X	X					X					X		X		X												X			

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

PART-5 - Treatment B (PF-07817883 with Midazolam): Detailed Sampling Schedule

Table 8. PART-5: PK Days (Day 1, Day 5, Day 10) in Treatment B

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Treatment Period on PK Days**																												**Notes**
Days Relative to Day 1	**Day 1**										**Day 5**										**Day 10**									
Planned Hours Post 1st Dose on that day	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	
Vital signs (respiratory rate, PR, BP)	X										X		X		X						X		X		X						• Refer to Section 8.3.2.
12-Lead ECG	X										X										X				X						
Study intervention administration																															
PF-07817883 (BID dosing)	X								X		X								X		X										
Midazolam											X										X										• Day 5 AM dosing in optional Cohort 12 only.
Blood samples for:																															
Safety laboratory (≥4h fasting)											X										X										
Retained Research Sample for Genetics (Prep D1)	X																														

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 8. PART-5: PK Days (Day 1, Day 5, Day 10) in Treatment B

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Treatment Period on PK Days**																												**Notes**
Days Relative to Day 1	**Day 1**										**Day 5**										**Day 10**										
Planned Hours Post 1st Dose on that day	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	
Plasma PK (PF-07817883)	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	• Post-dose samples on Day 5 may not be collected based on emerging PK data.
Midazolam											X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	• Day 5 PK samples in optional Cohort 12 only.
Urine samples for:																															
Urinalysis											X										X										

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

1.3.6. PART-6: SE

Table 9. PART-6: SE

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Periods 1-3**															**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Days 29-36**		• Follow-up to occur 28-35 days after administration of last dose of study intervention via telephone contact.
Hours After Dose			**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24h**	**48h**	**72h**	**96h**	**120h**			
Informed consent	X																			
Inclusion/exclusion criteria	X	X																		• Not required in Period 2 and Period 3.
Demographics (including height & weight)	X																			• Refer to Section 8.1.1.2.
Medical/Medicine history	X	X																		• Only required in Periods 2 and 3 if discharged from the site.
SARS-CoV-2 RT-PCR		X																		• Only required in Periods 2 and 3 if discharged from the site. • As per local CRU procedures.
COVID-19 signs and symptoms	X	X																		• As per local CRU procedures.
CRU Confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X			

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 9. PART-6: SE

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Periods 1-3															F/U Contact	E/T	Notes
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Days 29-36**		• Follow-up to occur 28-35 days after administration of last dose of study intervention via telephone contact.
Hours After Dose			**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24h**	**48h**	**72h**	**96h**	**120h**			
PE	X	X					X										X		X	• Full PE may be performed at Screening or admission in Period 1 only. Further full/limited PE at PI's discretion. • Limited PE targeted to neuro-muscular exam to be done prior to dosing and post-dose on Day 1, 2(±0.5) h and ~120h post-dosing.
Vital signs (respiratory rate, PR, BP)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	• Refer to Section 8.3.2.
12-Lead ECG (triplicate)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	• Singlet at screening. • Pre-dose (0h) on Day 1 triplicate measurement to be collected at approximately -1h, -0.5h and 0h per local procedure.
Continuous cardiac telemetry monitoring			X	→	→	→	→	→	→	→	X									• Baseline telemetry to be recorded for at least 2 hours between admission and prior to dosing in Period 1 only while awake (Section 8.3.3.1).
Contraception check	X	X															X	X	X	• Day -1 in first period only and Day 6 in last period only if not discharged.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 9. PART-6: SE

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Periods 1-3**																**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Days 29-36**		• Follow-up to occur 28-35 days after administration of last dose of study intervention via telephone contact.
Hours After Dose			**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24h**	**48h**	**72h**	**96h**	**120h**			
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
Study intervention administration																				
PF-07817883 or Placebo			X		X															Divided doses (3000 mg) to be administered at 0 and 1h
Moxifloxacin or placebo (open label)			X		X															Moxifloxacin at 0h and placebo at 1h post dose
Blood Samples for:																				
Pregnancy test (WOCBP only)	X	X															X		X	• Day -1 in first period only and Day 6 in last period only if not discharged.
Safety laboratory (≥4h fasting)	X	X											X	X		X	X		X	• Day 6 in last period only.
HIV, HBsAg, HBcAb and HCVAb	X																			
Serum FSH (post-menopausal females only)	X																			
Retained Research Samples for Genetics (Prep D1)			X																	• Only in Period 1. • If not collected on the designated collection day, collect at the next available time point.
Plasma Pharmacokinetics (PF-07817883)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Plasma Pharmacokinetics (Moxifloxacin)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 9. PART-6: SE

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Periods 1-3**															**F/U Contact**	**E/T**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Days 29-36**		• Follow-up to occur 28-35 days after administration of last dose of study intervention via telephone contact.
Hours After Dose			**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24h**	**48h**	**72h**	**96h**	**120h**			
Urine Samples for:																				
Drug screen testing	X	X																		• Not required in Period 2 or Period 3 if the participants were not discharged.
Urinalysis	X	X											X	X		X	X		X	• Day 6 in last period only.

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 current study is the FIH study of PF-07817883 in healthy adult participants. It is a 6-part study combining PART-1: SAD, PART-2: MAD, PART-3: RBA/FE, PART-4: ME, PART-5: DDI, and PART-6:SE. PART-1 and PART-2 will evaluate safety, tolerability and PK of single and multiple ascending oral doses of PF-07817883 in healthy adult participants, respectively. PART-2 of the study may also evaluate the safety, tolerability, and PK in Japanese and Chinese participants. PART-3 will evaluate RBA and FE of up to 2 new PF-07817883 oral formulations. PART-4 will evaluate the ME of PF-07817883 in healthy male participants. PART-5 will evaluate the effect of steady-state PF-07817883 on the PK of midazolam in healthy participants. PART-6:SE will evaluate safety, tolerability, and PK at SE in healthy participants.

Results from this study will inform the study design of the Phase 2/3 studies of PF-07817883 in COVID-19 patients.

2.2. Background

Disease Overview

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

COVID-19 manifests as a wide range of illnesses, from asymptomatic infection to severe pneumonia, ARDS, and death. While the majority of cases (approximately 80%) are asymptomatic or mild,[2] patients who are hospitalized with COVID-19 may have significant morbidity and mortality,[3,4] and are at increased risk of developing complications such as ARDS, acute cardiac injury, thromboembolic events and/or kidney injury.[5,6,7]

Current Treatment Options

Although monoclonal antibodies and antivirals have since become available there remains an important need to develop therapeutics for the treatment of COVID-19 infection. Several mAB became available under EUA, including bebtelovimab, for the treatment of mild to moderate COVID-19 infection in select populations. However, other mAB such as bamlanivimab with etesivimab and sotrovimab, have since been removed as treatment options due to diminished efficacy with the emergence of SARS-CoV-2 variants.[8] Antivirals such as nirmatrelvir/ritonavir and remdesivir IV are available and considered preferred therapy for nonhospitalized adults, while bebtelovimab and molnupiravir are considered alternative therapies by the COVID-19 Treatment Guidelines Panel.[9] However, these therapeutics are limited to outpatient populations with mild to moderate COVID-19 infection

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

at risk for progressing to severe disease. Furthermore, some high-risk patients may be ineligible for nirmatrelvir/ritonavir due to DDIs, and remdesivir may be inaccessible for some patients as it requires administration in a health care setting and returning for 3 subsequent days for daily IV dosing.

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

Rationale for Development of PF-07817883

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

Inhibition of the SARS-CoV-2 M^{Pro} by nirmatrelvir/ritonavir has demonstrated the efficacy of an antiviral in the reduction in hospitalization and death in mild to moderate COVID-19 patients with high risk of progression to severe disease.

2.2.1. Nonclinical Overview

2.2.1.1. Nonclinical Pharmacology

PF-07817883 is a potent (IC_{50} = CCI μM; Ki = CCI μM) and selective inhibitor of SARS-CoV-2 M^{pro}, exhibiting broad spectrum inhibitory activity against across the Coronaviridae family of M^{pro} enzymes. PF-07817883 binds to the active site of SARS-CoV-2 M^{pro} and forms a covalent interaction with Cys145. The key contact residues of M^{pro} that interact with PF-07817883 are highly conserved among alpha and beta coronavirus strains. PF-07817883 did not inhibit protease activity in a panel of mammalian proteases and was inactive against enterovirus 71 and human rhinovirus B, demonstrating its selectivity to the coronavirus family.

The in vitro antiviral activity of PF-07817883 against SARS-CoV-2 was demonstrated in several cell lines: a differentiated normal African green monkey kidney VeroE6 cells sorted for expression of higher levels of the ACE2 receptor, human adenocarcinoma derived alveolar basal epithelial cells constitutively expressing the human ACE2 receptor (A549-ACE2), and dNHBE cells. In all cellular systems tested, PF-07817883 demonstrates potent antiviral activity against SARS-CoV-2. In dNHBE cells, a physiologically relevant, primary human lung alveolar epithelial cell line, PF-07817883 inhibited SARS-CoV-2 viral

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

replication with an EC_{50} of 0.0343 µM and EC_{90} of 0.0699 µM after 3 days of drug exposure. PF-07817883 also exhibited antiviral efficacy against SARS-CoV-1, HCoV-229E, and MERS-CoV in cellular systems. In addition, PF-07817883 demonstrated antiviral activities against Alpha, Beta, Delta, Gamma, Lambda, Mu, and Omicron variants in the Vero TMPRSS2 and VeroE6 P-gp KO cells.

CCI [redacted]

More details are presented in the IB.

2.2.1.2. Biopharmaceutics and Nonclinical PK

2.2.1.2.1. 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/sec, indicating low passive permeability. Preliminary PBPK modeling predicts slight improvement (≤20%) in fraction absorbed in fed state compared to fasted state.

2.2.1.2.2. Nonclinical PK and In Vitro Metabolism

PF-07817883 exhibited moderate CL, with a moderate to low V_{ss} resulting in $t_{1/2}$ 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 the rat and monkey repeat dose toxicity studies, mean systemic exposures increased with increasing dose and no consistent sex-related differences were observed.

PF-07817883 exhibited low in vitro permeability and preferentially distributed into plasma relative to blood cells in all species evaluated. PF-07817883 was relatively unbound in rat ($f_{u,rat}$=0.927) and mouse ($f_{u,mouse}$=0.857) plasma. Concentration-dependent protein binding was observed in rabbits and monkeys, while no meaningful concentration-dependent binding was observed at ≤10 µM in humans. the 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]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CYP-mediated oxidation was the primary metabolic route of PF-07817883 in vitro and in rats. The primary metabolite across species (M1, PF-07832809) was derived from the hydroxylation at the 5-position of the pyrrolidone ring. In vitro studies in human liver microsomes indicated metabolism of PF-07817883 was predominantly mediated by CYP3A4 (CCI). PF-07817883 was the main drug-related entity in plasma, feces, and urine of rats receiving an oral dose of PF-07817883. Most metabolites were observed at trace levels in plasma and urine, and M1 was a primary metabolite in feces. The main route of hepatic clearance is anticipated to be via oxidative pathways with minor contributions from hydrolysis reactions. No unique human metabolites were observed.

In humans, PF-07817883 is predicted to have a plasma CL of 2.8 mL/min/kg and a V_{ss} of 1 L/kg with an effective $t_{½}$ of 4 hours.

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

More details are presented in the IB.

2.2.1.3. 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] over the predicted human unbound C_{max} and AUC_{24} at a dose of 730 mg BID.

In general, the nonadverse findings in the nonGLP exploratory studies and the GLP pivotal studies were similar. CCI [redacted]

More details are presented in the IB.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

2.2.2. Clinical Overview

C5091001 is the first clinical study using PF-07817883. As of data snapshot date of 18 January 2023, the evaluation of PART-1 and the dose escalation cohorts in PART-2 have completed. PART-4 evaluation is complete, but data were unavailable for inclusion in the data snapshot. PART-3 and PART-5 and the optional cohorts of Chinese participants and Japanese participants in PART-2: MAD are planned. As of data snapshot date, a total of 34 healthy adult participants were randomized and treated with PF-07817883 or placebo in PART-1 and PART-2. As the study is still ongoing, the summary of safety, tolerability and PK data presented here are preliminary and subject to change; however, the overall conclusions are not expected to change.

PART-1 included 2 interleaving cohorts with a total of 16 participants with 3-period cross-over in each cohort. For each period, up to 6 participants received a single oral dose of PF-07817883 and up to 2 participants received placebo. Single doses of PF-07817883 ranged from 150 mg to 4000 mg. Two participants in Cohort 1 were discontinued due to Physician's Decision [redacted] and Other [redacted] Two participants in Cohort 2 also discontinued due to Physician's Decision ([redacted] and Withdrawal by Participant ([redacted].

PART-2 included 3 cohorts evaluating safety, tolerability, and PK data up to 12 days at 200 mg, 600 mg and 1500 mg doses of PF-07817883 or placebo administered BID for up to 10 days. As of 18 January 2023, 18 participants were randomized in 3 cohorts in PART-2. One participant discontinued in Cohort 4 of PART-2 due to was Other ([redacted].

2.2.2.1. Safety Overview

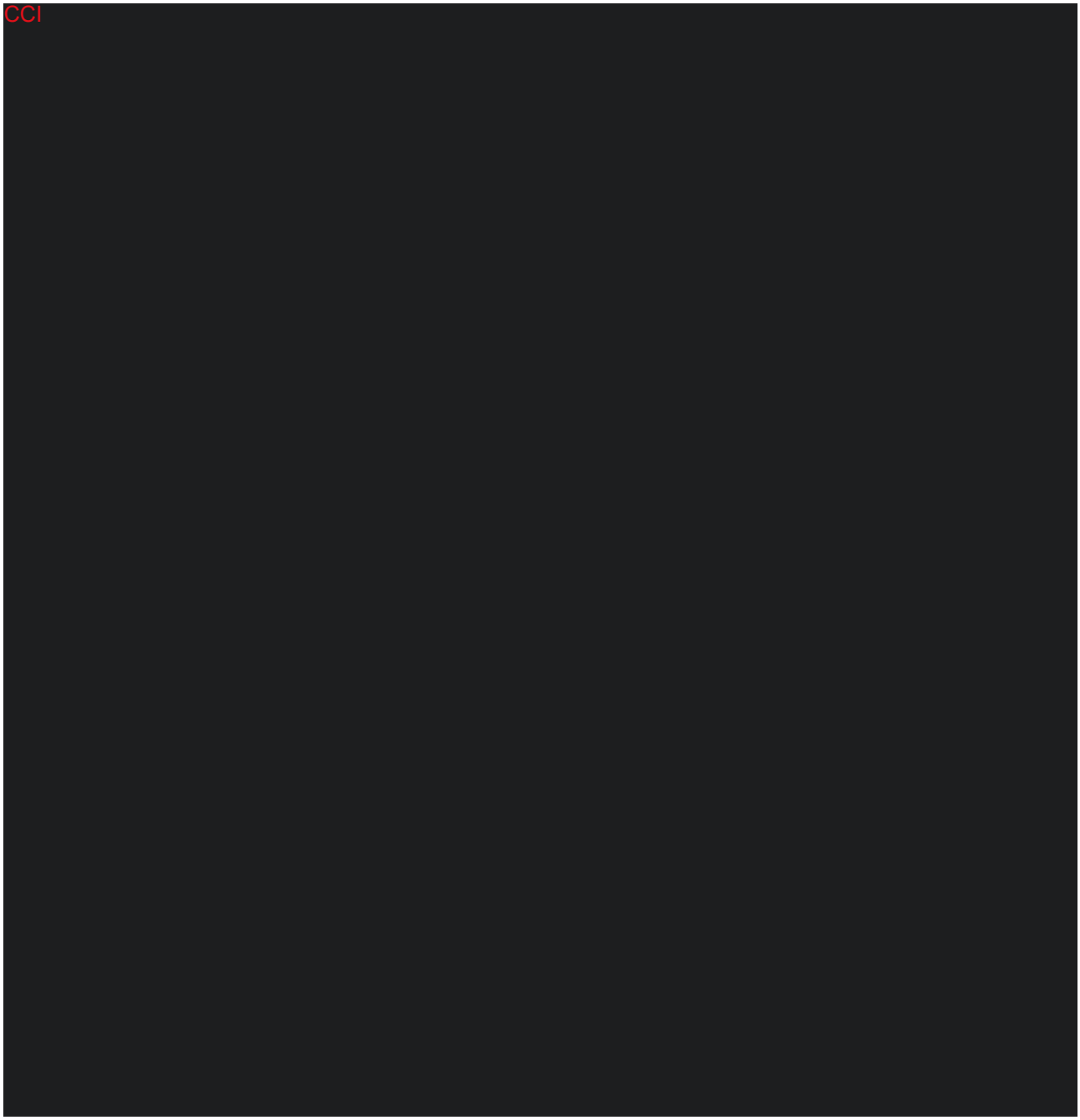
The preliminary data collected as of the data snapshot (18 January 2023) in PART-1 and PART-2 of the Phase 1 study (C5091001) demonstrated an acceptable safety profile at single doses of PF-07817883 or placebo ranging from 150 mg to 4000 mg in PART-1, and at doses of 200 mg to 1500 mg BID of PF-07817883 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. [redacted]

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

2.2.2.2. Summary of PF-07817883 PK in Human

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)



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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

2.3. Benefit/Risk Assessment

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

Study C5091001 is the first time that PF-07817883 will be administered to humans. For healthy participants participating in this study, no clinical benefit is expected. The purpose of the study is to provide the basis for further clinical development of PF-07817883 as a potential new, pharmacological agent for the treatment of participants with COVID-19. As of 14 September 2022, no specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.2.1.3. The clinical impact of these potential risks will be minimized through the proposed cautious dose-escalation process wherein higher doses of PF-07817883 will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile. In addition, this study includes standard, intensive, inpatient monitoring of the participants following administration of single, oral doses of the study intervention.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07817883 may be found in the IB, which is the SRSD for this study. The SRSD for the midazolam is the EU SmPC or USPI. The SRSD for moxifloxacin is the USPI.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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]		
Study Intervention(s): Midazolam		
Cardiac and respiratory effects (eg, respiratory depression, apnea, respiratory arrest and/or cardiac arrest, hypotension, changes in the HR, vasodilation effects, dyspnea, laryngospasm)	Adverse reactions reported following midazolam administration.	A single dose of 5 mg will be administered in the study. Participants will be monitored by vital signs, ECGs and AE collection in an inpatient CRU.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity reactions (eg, bronchospasm, anaphylactic shock, rash, urticaria, pruritus)	Adverse reactions reported following midazolam administration.	A single dose of 5 mg will be administered in the study. Participants will be monitored by vital signs and AE collection in an inpatient clinical research unit.
Neurological disturbances (eg, drowsiness and prolonged sedation, reduced alertness, mental confusion, euphoria, hallucinations, fatigue, headache, dizziness, ataxia, postoperative sedation, and anterograde amnesia)	Adverse reactions reported following midazolam administration.	A single dose of 5 mg will be administered in the study. Participants will be monitored by vital signs and AEs in an inpatient clinical research unit.
Paradoxical reactions (eg, agitation, involuntary movements (including tonic/clonic spasms and muscle tremors), hyperactivity, hostility, anger reactions, aggressiveness, paroxysmal excitement, and violent actions)	Adverse reactions reported following midazolam administration.	A single dose of 5 mg will be administered in the study. Participants will be monitored by vital signs and AEs collection in an inpatient clinical research unit.
Gastrointestinal disturbances (eg, nausea, vomiting, hiccups, constipation, dry mouth)	Adverse reactions reported following midazolam administration.	A single dose of 5 mg will be administered in the study. Participants will be monitored by vital signs and AEs collection in an inpatient clinical research unit.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): Moxifloxacin		
Gastrointestinal disturbances (eg, nausea, diarrhoea, vomiting)	Adverse reactions reported following moxifloxacin administration	A single dose of 400 mg will be administered in the study. Participants will be monitored for AEs in an inpatient clinical research unit.
Hypersensitivity reactions, including anaphylactic reactions	Adverse reactions reported following moxifloxacin administration	A single dose of 400 mg will be administered in the study. Participants will be monitored by vitals and for AEs in an inpatient clinical research unit. Participants with history of hypersensitivity or intolerance to quinolone antibiotics, including moxifloxacin, will be excluded.
Peripheral neuropathy, exacerbation of myasthenia gravis, and central nervous system effects including agitation, insomnia, dizziness and anxiety.	Adverse reactions reported following moxifloxacin administration	A single dose of 400 mg will be administered in the study. Participants will be monitored for AEs in an inpatient clinical research unit. Participants with history of myasthenia gravis are excluded.
Tendinitis and tendon rupture	Adverse reaction reported following moxifloxacin administration	A single dose of 400 mg will be administered in the study. Participants will be monitored for AEs in an inpatient clinical research unit.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Prolongation of the QT interval and isolated cases of torsade de pointe	Adverse reaction reported following moxifloxacin administration	A single dose of 400 mg will be administered in the study. Participants will be monitored for cardiac changes (telemetry and ECG) and AEs in an inpatient clinical research unit. Participants with known history or risk factors for prolonged QT will be excluded.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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.

3. OBJECTIVES AND ENDPOINTS

3.1. PART-1: SAD

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability following single ascending doses of PF-07817883.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.
Secondary:	**Secondary:**

• To assess the plasma PK profile of PF-07817883 following single ascending doses of PF-07817883.	• Plasma PK parameters of PF-07817883:
	  • C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn).
	  • If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.

Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To explore metabolites in plasma, urine, and feces, if data permit.	• Qualitative characterization of metabolites of PF-07817883 in pooled plasma, urine, and feces if data permit.
• To determine the extent of excretion of drug-related material in urine and feces after a single oral administration of PF-07817883.	• Total recovery of drug-related material in urine and feces separately, and both routes combined, expressed as a percent of total dose administered.
• To evaluate the effect of food (high-fat meal) on the exposure of PF-07817883 following a single oral dose of PF-07817883, if evaluated (Optional).	• The ratio of AUC_{last}, AUC_{inf} (if data permit) and C_{max} under fed condition and fasted condition.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

3.2. PART-2: MAD (including optional Japanese and Chinese Cohort)

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability following multiple ascending doses of PF-07817883.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.
Secondary:	**Secondary:**

• To assess the plasma PK profile of PF-07817883 on Days 1, 5 and 10 following multiple ascending doses of PF-07817883.	• Plasma PK parameters of PF-07817883:
	  • C_{max}, T_{max}, AUC_{tau}, C_{12}, $C_{max}(dn)$, $AUC_{tau}(dn)$, C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR,CL/F and V_z/F.
	  • If data permit, $t_{½}$.

• To assess the renal excretion of PF-07817883 on Day 10 following multiple ascending doses of PF-07817883.	• PF-07817883 urinary PK parameters: • Ae_{tau} and Ae_{tau}%, CL_r.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To explore PK by microsampling technique(s), if evaluated (Optional).	• Concentration of PF-07817883, if evaluated.
• To explore RBC partitioning of PF-07817883 (Optional).	• Ratio of PF-07817883 concentration in plasma to that in blood.
• To explore the effect of PF-07817883 on endogenous plasma biomarkers. (Optional)	• Ratio of plasma concentrations of endogenous biomarkers on Day 10 to those before PF-07817883 dose.

3.3. PART-3: RBA/FE

Objectives	Endpoints
Primary:	**Primary:**
• To determine the oral bioavailability of oral formulation(s) of PF-07817883 relative to suspension.	• The ratio of AUC_{last}, AUC_{inf} and C_{max} of oral formulation(s) and suspension.
Secondary:	**Secondary:**
• To evaluate the effect of food (high-fat high-calorie meal) on the exposure of PF-07817883 following a single oral dose of PF-07817883 tablet formulation(s).	• The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation under fed condition and fasted condition.
• To determine the PK of PF-07817883 following oral administration of tablet formulation(s) and suspension of PF-07817883.	• Plasma PK parameters of PF-07817883: $T_{max,}$ $C_{max,}$ AUC_{last}, if data permit AUC_{inf}, $t_{½}$, CL/F, V_z/F.
• To determine the safety and tolerability of PF-07817883 following oral administration of tablet formulation(s) and suspension of PF-07817883.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To evaluate the taste attributes of the PF-07817883 following oral administration of oral formulation(s) and suspension of PF-07817883.	• Taste Assessment Survey Scoring Metrics: mouth feel, bitterness, tongue/mouth burn, throat burn, overall liking.

3.4. PART-4: ME

Objectives	Endpoints
Primary:	**Primary:**
• To determine the extent of excretion of drug-related material in urine and feces after a single oral administration of PF-07817883.	• Total recovery of drug-related material in urine and feces separately, and both routes combined, expressed as a percent of total dose administered.
Secondary:	**Secondary:**
• To determine the PK of PF-07817883 following a single oral administration of PF-07817883.	• Plasma PK parameters of PF-07817883: T_{max}, C_{max}, AUC_{last}, if data permit AUC_{inf}, $t_{½}$, CL/F, V_z/F.
• To determine the safety and tolerability of PF-07817883 after a single oral administration of PF-07817883.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of PF-07817883, if possible.	• Metabolic profiling/identification and determination of relative abundance of PF-07817883 and the metabolites of PF-07817883 in plasma, urine, and feces, if possible.

3.5. PART-5: DDI

Objectives	Endpoints
Primary Objective:	**Primary Endpoint:**
• To estimate the effect of PF-07817883 on the PK of midazolam.	• Midazolam plasma PK parameters: C_{max} and AUC_{inf} (if data permit, otherwise AUC_{last}) with PF-07817883 (test) versus without PF-07817883 (reference).
Secondary Objective:	**Secondary Endpoints:**
• To evaluate the safety and tolerability of PF-07817883 in healthy participants in the absence and presence of midazolam.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.
• To evaluate the effects of PF-07817883 on additional PK parameters of midazolam in healthy participants.	• Midazolam plasma PK parameters: T_{max}, AUC_{last}, and if data permit $t_{½}$, CL/F, and V_z/F for midazolam with and without coadministration of PF-07817883.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Objectives	Endpoints
Tertiary/Exploratory Objectives:	**Tertiary/Exploratory Endpoints:**
• To assess the plasma PK profile of PF-07817883 on Days 1, 5 (optional) and 10 following multiple ascending doses of PF-07817883.	• Plasma PK parameters of PF-07817883: • C_{max}, T_{max}, AUC_{tau}, C_{12}, C_{max}(dn), AUC_{tau}(dn), C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR,CL/F and V_z/F. • If data permit, $t_{½}$.
• To assess the plasma PK profile of PF-07817883 on Days 1, 5 (optional) and 10 following multiple ascending doses of PF-07817883 in Chinese and Japanese participants (Optional).	• Plasma PK parameters of PF-07817883: • C_{max}, T_{max}, AUC_{tau}, C_{12}, C_{max}(dn), AUC_{tau}(dn), C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR,CL/F and V_z/F. • If data permit, $t_{½}$.

3.6. PART-6: SE

Objectives	Endpoints
Primary Objective:	**Primary Endpoint:**
• To assess the safety and tolerability of a SE of PF-07817883 administered as split dosing.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.
Secondary Objective:	**Secondary Endpoints:**

• To assess the plasma PK of PF-07817883 at an SE of PF-07817883 administered as split dosing.	• Plasma PK parameters of PF-07817883:
	  • C_{max}, T_{max}, AUC_{last}
	  • If data permit, AUC_{inf}, $t_{½}$.

Exploratory Objectives:	**Exploratory Endpoints:**
• To assess the plasma PK of moxifloxacin.	• Plasma moxifloxacin parameters C_{max}, T_{max} and AUC_{last}.
• To determine assay sensitivity by comparing the effect of moxifloxacin 400 mg on QTcF interval with placebo at historical moxifloxacin Tmax of 3 hours.	• Time matched mean differences in QTcF between moxifloxacin and placebo at the historical moxifloxacin Tmax of 3 hours.
• To determine assay sensitivity by exposure-response analysis of moxifloxacin	• Baseline corrected QTcF
• To determine exposure response analysis of PF-07817883	• Baseline corrected QTcF

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

4. STUDY DESIGN

4.1. Overall Design

This study may be conducted at sites in the US and/or EU.

This 6-part, Phase 1, FIH study will combine PART-1: SAD, PART-2: MAD (including optional Japanese and Chinese Cohorts), PART-3: RBA/FE, PART-4: ME, PART-5: DDI and PART-6: SE. Study schema is shown in Section 1.2. PART-1 and PART-2 are a randomized, double-blind, sponsor -open, placebo-controlled study to evaluate safety, tolerability, and PK of single and multiple escalating oral doses of PF-07817883 in healthy adult participants, respectively. PART-2 of the study may also evaluate the safety, tolerability, and PK in Japanese and Chinese participants. PART-3 is a randomized, open-label, cross-over, study to evaluate RBA and FE of 2 new PF-07817883 oral formulations. PART-4 is an open-label, non-randomized, single period to evaluate the ME of PF-07817883. PART-5 is an open-label, randomized, cross-over study to evaluate the effect of steady-state PF-07817883 on PK of midazolam in healthy adult participants. PART-6: SE is a sponsor-open, randomized, 3-treatment, 3-period, 6-sequence, cross-over, placebo-and positive-controlled study to evaluate safety, tolerability, and PK at SE in healthy participants.

PART-1: SAD,dose escalation cohorts (Cohorts 3, 4, 5 and 6) in PART-2: MAD and PART-6: SE will be conducted at NH CRU only. The optional Japanese and Chinese cohorts in PART-2: MAD, PART-3: RBA/FE, PART-4: ME and PART-5: DDI may be conducted at NH CRU or BR CRU and will only be initiated after the safety and PK is established in dose escalation cohorts at the same or higher dose of PF-07817883.

In all 6 parts, participants will be screened within 28 days of their first dose of study intervention. Participants will be admitted to the CRU on Day -1 or earlier and may be discharged at investigator discretion following completion of assessments per the SoA. In PART-4, participants may be admitted earlier to facilitate collection of pre-dose fecal sample. If a participant has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

Participants who discontinue for non-safety related reasons prior to completion of the study may be replaced, at the discretion of the PI and sponsor. The replacement participant(s) may or may not be required to complete all periods of the cohort in which they are participating at the discretion of the PI and sponsor.

In PART-1 and PART-2 of the study, the dose levels, frequency of administration and/or meal condition may be changed based on emerging PK and safety data. During the SAD and MAD the dose increments and planned doses may be adjusted, as the study progresses dependent upon emerging PK, safety, and tolerability data. Other intermediate doses or lower doses may be administered instead of the planned doses, or changes in dosing frequency or titration schemes may be proposed for MAD cohorts if safety/tolerability or PK issues

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

become apparent, if evidence of nonlinear PK dictates the need to escalate more slowly, or if subsequent doses are predicted to result in exposures that exceed the target limits. Any potential altered dose scheme will be equal to or less than a 3.3-fold increase in exposure from the previous highest dose if a higher dose is warranted to achieve exposure. If gastrointestinal tolerability issue becomes dose-limiting in PART-1 or PART-2, dosing with food (standard meal) or pre-dosing with anti-emetics may be considered. The projected average exposure of the altered dose scheme will not exceed the exposure limit specified in Section 6.6.1. The total daily dose in PART-1 and PART-2 will not exceed 6000 mg. The dose escalation will stop if the dose escalation stopping criteria are met as specified in Section 6.6.1.

In all cohorts (all parts of the study), participants can be released after completing activities specified in the SoA. A telephone follow-up contact will occur between 28 and 35 days after the day of last administration of study intervention. At the discretion of the investigator, telephone follow-up contact may be substituted with an on-site visit in case of additional follow-up of open AEs or clinically significant laboratory findings.

The total planned duration of participation, from Screening visit to the Follow-up phone call, may be up to 10, 10, 9, 8, 11, and 10 weeks for PART-1, PART-2, PART-3, PART-4, PART-5, and PART-6, respectively.

At the discretion of the sponsor and investigator, participants who were enrolled in PART-1 or PART-2 may be enrolled in other parts of the study.

4.1.1. PART-1: SAD

SAD will include 2 interleaving cohorts with a total of approximately 16 participants planned (approximately 8 participants in each cohort – 6 active: 2 placebo), with 3-period, cross-over in each cohort. Period 3 is an optional period which may be used to further explore PK at additional doses or assess FE (high-fat high-calorie meal), based on emerging safety, tolerability, and PK assessments. For each period, approximately 6 participants will receive a single oral dose of PF-07817883, and approximately 2 participants will receive placebo after at least 10 hours of fasting. In order to improve gastrointestinal tolerability, if required based on emerging safety data, PF-07817883 may also be dosed with standard meal (Section 5.3.2). If required to be dosed in fed state, the participants will be required to eat a meal before drug administration as specified in Sections 5.3.2 and 6.1. Each participant may receive either a single dose of PF-07817883 or a placebo during each period. In each period, participants on active treatment in Cohort 1 and Cohort 2 will receive dose levels in dose escalation format as specified in provisional dosing scheme shown in Table 11. Except D1 of Cohort 1 in SAD, all other dose levels and/or meal condition may be changed based on emerging PK and safety data. Dose escalation to subsequent dose levels in SAD cohorts will be based on all available (a minimum of 48 hours post-dose) safety data and PK over approximately ≥6 hours in a minimum of 4 participants (3 active and 1 placebo) at previous dose levels.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 11. Provisional Dosing Scheme in PART-1: SAD

	N	Period 1	Period 2	Period 3[a]
Cohort 1	N=2	Placebo (PL)	D3	D5
	N=2	D1	PL	D5
	N=2	D1	D3	D5
	N=2	D1	D3	PL
Cohort 2	N=2	PL	D4	TBD
	N=2	D2	PL	TBD
	N=2	D2	D4	TBD
	N=2	D2	D4	TBD

Dose levels are specified in Table 15, Section 4.3.

a. Period 3 is optional and may be used for evaluation of additional dose levels or FE. Period and dose levels for FE may be changed based on emerging PK data. If FE conducted in Period 3, the active/Placebo allocation will be the same as equivalent dose used in Periods 1 or 2.

There will be a washout interval of ≥5 days between dosing to a given participant. Participants will be required to stay at the CRU for the duration of the washout interval. However, they may be released at the discretion of the investigator. The washout interval may be adjusted based on data emerging from previous cohorts/periods.

Optional Period 3 of Cohorts 1 or 2 may be used to explore FE (high-fat high-calorie meal) or additional doses. If conducted, the active/Placebo allocation will be the same as equivalent dose used in Periods 1 or 2.

The urine and feces may be collected for 5 days as specified in the SoA for the measurement of total drug-related material and metabolite profiling at the provisional dose levels D3 and D4. Based on the emerging PK data, the dose level for urine and feces collection may be changed. Dietary fiber supplementation and use of laxative (Section 5.3.2.1) should be considered with the goal to facilitate at least once daily bowel movement for urine and feces collection. The use of the laxative should be recorded.

4.1.2. PART-2: MAD

The first MAD cohort may start after a total daily dose, which provides comparable or higher total daily exposure (24h) in SAD to the projected total daily steady-state exposure (over 24h) at the starting dose in MAD, is found safe and well tolerated in PART-1 of the study. The proposed MAD study design will be parallel cohorts, with 10 days of dosing. PART-2 will consist of approximately 2 to 6 cohorts including up to 4 optional cohorts (Cohorts 5, 6, 7 and 8) with approximately 6 participants in each cohort (4 active: 2 placebo). Cohorts 7 and 8 are optional Japanese and Chinese participants, respectively. In each cohort, approximately 4 participants will receive 1 of the escalating doses of PF-07817883 as specified in Table 16 (Section 4.3) and approximately 2 participants will receive matching placebo after at least 10h of fast for the morning dose and 2h of fast for the evening dose. From Day 1-Day 9, PF-07817883/placebo will be administered every 12h (ie, BID). On Day 10, PF-07817883/placebo will be administered at approximately 0h in the morning only with no dosing in the evening. If required to be dosed in fed state, the participants will be required to

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

eat a meal before drug administration (as specified in Sections 5.3.2 and 6.1). Dose escalation to subsequent dose levels in MAD cohorts will be based on a minimum of 6 days safety data and PK over approximately ≥6 hours on Day 5 in a minimum of 4 participants (3 active and 1 placebo) at previous dose levels.

Safety, tolerability, and PK may be evaluated in Japanese and Chinese participants as defined in Sections 5.1 and 5.2 after multiple oral administration of PF-07817883 in PART-2. If conducted, these cohorts will have all evaluations as specified in the SoA for MAD cohorts and the dose level in this cohort will be equal or lower than the highest dose level already evaluated in healthy Western participants. Frequency of administration and meal condition will be based on safety, tolerability, and PK data from MAD cohorts.

Changes in plasma PK biomarkers such as cholesterol, hydroxycholesterol etc, may be explored. If possible, microsampling PK and RBC partitioning, and/or metabolite profiling may also be done.

4.1.3. PART-3: RBA/FE

This cohort will be an open-label, randomized, 4-period, 6-sequence cross-over SD cohort evaluating the RBA of 2 new PF-07817883 oral formulation(s) compared to PF-07817883 oral suspension and to evaluate the effect of food on the bioavailability of the PF-07817883 oral formulation(s) in healthy adult participants. An exploratory assessment of the taste (Appendix 9) may be conducted. Approximately 12 participants will be enrolled in PART-3 of the study with approximately equal number of participants randomized to 1 of 6 sequences (Table 12).

Table 12. Treatment Sequences in PART-3: RBA/FE

Sequence	Period 1	Period 2	Period 3	Period 4
1	A	B	C	D
2	B	C	A	D
3	C	A	B	D
4	B	A	C	E
5	A	C	B	E
6	C	B	A	E

Treatment A = PF-07817883 600 mg oral suspension SD Fasted;
Treatment B = PF-07817883 600 mg Formulation 1 [redacted] Fasted
Treatment C = PF-07817883 600 mg Formulation 2 [redacted] Fasted
Treatment D = PF-07817883 600 mg Formulation 1 [redacted] Fed (high-fat meal)
Treatment E = PF-07817883 600 mg Formulation 2 [redacted] Fed (high-fat meal)

In this part, there will be a washout interval of at least 3 days between dosing to a given participant in each period. Participants will be required to stay at the CRU until the discharge in the last period.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

4.1.4. PART-4: ME

This part will include a single cohort of approximately 6 male participants. The dose of this cohort will be decided based on the emerging PK and safety data. The selected dose will not exceed the highest dose deemed safe in PART-1. Each participant will receive a single dose of PF-07817883 at 0 hr on Day 1 along after at least 10 hr of fasting. The plasma for PK and metabolic profiling will be collected as specified in the SoA. The urine and feces will be collected for 10 days after dosing as specified in SoA to determine excretion routes and metabolite profiling. A fecal sample is required prior to dosing on Day 1. Dietary fiber supplementation and use of laxative (Section 5.3.2.1) should be considered with the goal to facilitate at least once daily bowel movement. The use of the laxative should be recorded. The participants will be discharged on Day 11.

4.1.5. PART-5: DDI

This part may consist of up to 2 cohorts (Cohort 11 and optional Cohort 12). Based on the data from the Cohort 11, an optional Cohort 12 may be initiated at a dose lower than the 600 mg BID. Both cohorts will have 2 treatments, 2 sequences, and 2 periods with a cross-over design to evaluate the effect of steady-state PF-07817883 on the PK of midazolam in healthy adult participants. The dose of PF-07817883 in Cohort 11 is 600 mg BID and dose of optional Cohort 12 will be decided based on the emerging PK data from Cohort 11. The 2 sequences are considered to estimate the sequence effect due to differences in the treatment sequence and the differences in dosing duration. Each enrolled participant will be randomly assigned to 1 of 2 sequences to receive 2 treatments in 2 periods. The 2 treatments in this part will be: single oral dose of 5 mg midazolam alone (Treatment A) and multiple oral doses of PF-07817883 in combination with a single oral dose of 5 mg midazolam (Treatment B). In Treatment B, PF-07817883 will be administered every 12h (ie, BID) from Day 1 – Day 9 and PF-07817883 along with 5 mg midazolam will be administered at approximately 0h in the morning on Day 5 (only for optional Cohort 12) and Day 10. For Treatment B, intensive PK samples are planned on Day 1, Day 5 and Day 10. If required to be dosed in fed state, the participants will be required to eat a meal before drug administration (as specified in Sections 5.3.2 and 6.1). A washout of at least 2 and 7 days is required after Treatment A and Treatment B, respectively.

A total of approximately 14 healthy participants will be enrolled in each cohort to ensure at least 12 participants will complete that cohort. Participants who discontinued from this part for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the investigator. At the discretion of the sponsor, Japanese and Chinese participants may be enrolled in this part to assess PK and safety of PF-07817883 in these ethnic groups.

Enrolled participants in each cohort will be randomly assigned to 1 of 2 sequences to receive 2 treatments in 2 periods as in Table 13. Participants will be discharged following completion of all assessments as specified in the SoA in Period 2.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 13. Treatment Sequences in PART-5: DDI

	Period 1	Period 2
Sequence 1 (n=7)	Treatment A	Treatment B or Treatment C
Sequence 2 (n=7)	Treatment B or Treatment C	Treatment A

- Treatment A: Single oral dose of 5 mg midazolam with at least 2-day washout (Treatment A period duration: Day 1 to Day 3).
- Treatment B: PF-07817883 administered orally for 10 days: Day 1 morning to Day 10 morning. On Day 10 morning, participants will receive a single oral dose of 5 mg midazolam administered with PF-07817883, followed by a 7-day washout (Treatment B period duration: Day 1 to Day 17).
- Treatment C: PF-07817883 administered orally for 10 days: Day 1 morning to Day 10 morning. On Day 5 morning and Day 10 morning, participants will receive a single oral dose of 5 mg midazolam administered with PF-07817883. A 7-day washout to follow after last PF-07817883 administration (Treatment C period duration: Day 1 to Day 17).

4.1.6. PART-6: SE

This is a single-dose, randomized, 3-treatment, 3-period, cross-over, 6-sequence, sponsor-open, placebo-and positive-controlled study to be conducted in approximately 24 adult healthy participants. Each participant will be randomly assigned to one of the treatment sequences shown in Table 14. The participants randomized to treatment will receive 6000 mg as 2 split doses of PF-07817883 3000 mg administered at 0 and 1 h. The participant randomized to placebo will receive placebo at 0 and 1h. The participants randomized to moxifloxacin will receive moxifloxacin 400 mg and placebo at 0 and 1h, respectively. Treatment assignments to PF-07817883 and placebo will be blinded to the participants, investigator and CRU staff (except pharmacy staff) but open to the sponsor. Administration of moxifloxacin and placebo in participants randomized to moxifloxacin treatment will be open label. Each period will be separated by at least 7 days of wash-out interval.

Sentinel dosing will be implemented such that 3 participants will be administered with 1 each receiving Treatment A, B or C on Day 1 in Period 1. The following day, safety data up to 24 hours post-dose for these participants (including assessment of AEs, vitals, ECGs, and telemetry) will be reviewed by the PI prior to dosing the additional 3 participants with 1 each on Treatment A, B or C in Period 1. The dosing of the first 6 participants in Period 2 will commence upon review of safety data (including assessment of AEs, vitals, ECGs, telemetry, and the laboratory assessment at least up to 48h post-dose) from these 6 participants by the PI, if any of the stopping criteria as defined in Section 7.4.1 for sentinel dosing is not met. In subsequent periods (Period 2 and 3), at the discretion of the investigator, dosing may continue as done in Period 1 or all 6 participants may be dosed simultaneously with 2 each on Treatment A, B and C in each period.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Following the review of safety data including assessment of AEs, vitals, ECGs, and laboratory assessment (at least up to 48h post-dose in Period 3) of the first 6 participants, the dosing of additional participants may be initiated if any of the stopping criteria as defined in Section 7.4.2 is not met.

Table 14. Treatment Sequences in PART-6: SE

Sequence	Period 1	Period 2	Period 3
Sequence 1 (n=4)	A	B	C
Sequence 2 (n=4)	B	C	A
Sequence 3 (n=4)	C	A	B
Sequence 4 (n=4)	B	A	C
Sequence 5 (n=4)	A	C	B
Sequence 6 (n=4)	C	B	A

Treatment A: PF-07817883 6000 mg oral suspension administered as 2 split-doses of 3000 mg at 0 and 1h in fasted state.

Treatment B: Placebo oral suspension.

Treatment C: Moxifloxacin 400 mg SD at 0h and placebo at 1h in fasted state.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

4.2. Scientific Rationale for Study Design

Given the current study is the first to dose PF-07817883 to healthy participants, an escalating SD design with careful assessment and ongoing review of safety and PK data of PF-07817883 is planned. The 6-part FIH study including SAD, MAD, RBA/FE, ME DDI and SE design was planned to provide an opportunity to shorten the drug development timeline, without compromising the safety of the participants.

Males and females of 18-60 years of age was selected to better represent the COVID-19 patient population. PF-07817883 is a non-genotoxic but its effect on embryo-fetal development is currently not known. Therefore, both male and female participants are required to follow contraception requirements as specified in Section 5.3.1 and Appendix 4.

CCI [redacted]

4.2.1. PART-1: SAD

The cross-over design will permit both a within and between participant assessment of safety, tolerability, and PK. Furthermore, 2 interleaving cohorts will permit assessment of safety and PK over a wider dose range within a given participant compared to a sequential cohort design. To permit an unbiased assessment of safety, the administration of active versus placebo in each period will be double blinded to site staff (except those involved in preparation of doses) as well as the study participants.

For a given participant, dosing will be separated by ≥5 days. This planned dosing interval is deemed sufficient to permit washout of previous treatment. CCI [redacted]

At selected doses, the urine and feces may be collected to calculate total excretion of drug-related material using ^{19}F-NMR technique and understand metabolic profile as described in previous publications.[10]

4.2.2. PART-2: MAD

The safety and tolerability will be collected up to 12 days to evaluate the impact of PF-07817883 on relatively longer dosing; however, the dose escalation decision will be based on Day 5 PK. PBPK simulations (including induction and reversible inhibition potential) showed that the PK concentration after 5 days of dosing is expected to be very close to the steady-state. Therefore, the Day 5 PK and all available safety will be used to dose escalate to the next cohort in order to rapidly collect the PK and safety data to initiate the study in COVID-19 patients. By Day 10, the PK of PF-07817883 is expected to achieve steady-state and therefore, the steady-state plasma and urine PK will be determined on Day 10.

Exploratory dry blood microsampling PK sample and RBC partitioning sample may be collected to evaluate the microsampling techniques which may be employed in future clinical trials. Exploratory endogenous plasma PK biomarkers such as 4-β-hydroxycholesterol/cholesterol ratio, CP-1 etc. will be collected to understand the potential effect of PF-07817883 on metabolic enzyme and/or transporters.

4.2.3. PART-3: RBA/FE

This part of the study will evaluate bioavailability of up to 2 solid oral dose formulations (eg, tablet) relative to the formulation used in PART-1 and/or PART-2 of the study and explore the FE on the PK of new formulation(s) in healthy participants.

CCI [redacted]

To aid in the future development of a potential pediatric dosage form of PF-07817883 and assess the after taste profile of PF-07817883, PART-3 may assess the taste profile using a questionnaire (Appendix 9) at times specified in the SoA.

4.2.4. PART-4: ME

This part is an open-label, non-randomized, single period cohort to evaluate the ME of PF-07817883 in healthy male participants. Only males will be included in this study given the desire to enroll a homogeneous population due to the small sample size.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

A single dose of PF-07817883 is considered appropriate as available data do not indicate PF-07817883 PK are time-dependent, and hence, single dose data are considered predictive of steady-state.

The urine and feces samples collected will only be analyzed to determine the amount of drug-related material excreted. Considering the half-life and variability in gastrointestinal transit time, feces and urine will be collected up to 10 days after dosing to allow near complete collection of the drug or drug-related materials.

4.2.5. PART-5: DDI

This part is open-label to estimate the effect of steady-state PF-07817883 on the PK of midazolam in healthy adult participants.

CCI [redacted]. Based on half-life of CYP3A4 of approximately 29 h,[11] a 10 day treatment with PF-07817883 is sufficient to allow the concentration of PF-07817883 and CYP3A4 activity level to achieve steady-state. Subsequently, a 7-day washout period allows the CYP3A4 activity to return to baseline.

The 2 cohort design will allow up to 2 dose levels of PF-07817883 to be evaluated. A single dose midazolam is considered sufficient to estimate the potential induction effect of PF-07817883. Given 2-7 h half-life of oral midazolam, PK sampling is deemed sufficient to characterize PK profile of midazolam.

4.2.6. PART-6: SE

This part is a double-blind, sponsor-open, randomized, 3-period, 6-sequence, cross-over cohort to evaluate safety, tolerability, and PK at SE. The highest PF-07817883 dose currently planned to be evaluated in the Phase 2b study is 600 mg BID. CCI [redacted]

In SAD, the increase in exposure of PF-07817883 was limited by saturation of absorption at 3000 mg. In this cohort, PF-07817883 will be administered into split doses at time around expected T_{max} to achieve higher C_{max} of PF-07817883.

Extensive PK and triplicate ECGs are collected to enable potential exposure-response modeling with PF-07817883 concentration and ECG parameters. The cross-over, randomized design provides an intrasubject comparison of placebo for exposure-response analysis using PF-07817883 concentration and ECG parameters. Considering half-life and inter-individual variability in PART-1 of this study, a wash out of ≥7 days was deemed sufficient.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Sentinel dosing has been implemented as additional safeguards to ensure safety of the participants.

In this part of the study, moxifloxacin will be used as the active control for the measurement of effect on QT prolongation. An exposure response relationship of moxifloxacin may be used for assay sensitivity. Moxifloxacin is a fluoroquinolone antibiotic that produces consistent and predictable QT prolongation. Encapsulation of commercially available moxifloxacin tablets to achieve blinding has the potential to have an impact on absorption, therefore encapsulation will not be employed and moxifloxacin will be administered in an unblinded manner.

The sampling time points have been chosen based on the expected PK profiles of PF-07817883 and moxifloxacin. The time to reach maximum concentration (T_{max}) for PF-07817883 is approximately CCI post-dose based on PART-1 and PART-2 of this study. This schedule will also allow peak QT effects with moxifloxacin, which have been historically observed at 1 to 4 hours post-dose.

4.2.7. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of PF-07817883 have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.8. Collection of Retained Research Samples

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

4.3. Justification for Dose

4.3.1. Justification of Dose for PART-1 to PART-5 (Original Protocol, 14 September 2022)

The approach for dose selection for this study includes consideration of all relevant information obtained in non-clinical pharmacology and toxicity studies with PF-07817883.

Similar to nirmatrelvir, PF-07817883 is expected to exhibit therapeutic anti-SARS-CoV-2 activity in patients when the free plasma exposure is maintained at or above the in vitro EC_{90} values. The primary HAE cell assay is considered the most relevant for translation and has an EC_{90} value of CCI nM (≈CCI ng/mL free concentration CCI ng/mL total plasma concentration, observed geometric mean $f_{u,human}$ = CCI , which was considered the target C_{eff}.

The human PK of PF-07817883 after single and multiple dose administration was predicted using PBPK modeling by scaling in vitro hepatic clearance obtained from HLM in Simcyp® Version 21 release 1 (Certara, Sheffield, UK). The predicted plasma CL and V_{ss} of PF-07817883 are CCI mL/min/kg and CCI L/kg, respectively, providing an effective $t_{½}$ of approximately CCI hours.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI [redacted] For safety margin calculations (Table 15 and Table 16), the unbound fraction was model predicted.

The nonclinical safety profile of PF-07817883 has been adequately characterized in rats and non-human primates to support the progression into human clinical studies of up to 14 days of dosing. In cynomolgus monkeys and rats, NOAEL was established at CCI [redacted] mg/kg/day. Based on the lower systemic exposure, rat was considered the most sensitive species to set PK stopping criteria. The daily NOAEL exposure in rat was CCI [redacted] µg•h/mL and CCI [redacted] µg/mL for $AUC_{24,ss}$ and C_{max}, respectively. Based on rat NOAEL, after accounting for species differences in plasma protein binding [model predicted free fraction at C_{av} ($f_{u,human,cav}$)=CCI [redacted], assumed free fraction at C_{max} ($f_{u,human,cmax}$) CCI [redacted] fraction unbound in rat ($f_{u,rat}$)=CCI [redacted], PK stopping limit in human is defined as total plasma AUC_{24} and C_{max} of CCI [redacted] µg•h/mL and CCI [redacted] µg/mL, respectively.

The planned starting dose of PF-07817883 as a single dose is 150 mg. Being an anti-viral agent, the target (M^{Pro}) is not expressed in healthy participants hence primary pharmacology-related effect is not expected in healthy participants. The projected average free concentration ($C_{average,free}$) of approximately CCI [redacted] at 150 mg is more than CCI [redacted] times lower than the observed IC_{50} (IC_{50} CCI [redacted] µM) in off-target pharmacology screening panel. The projected total C_{max} and the AUC_{24} of PF-07817883 at the proposed starting dose of 150 mg is CCI [redacted] µg/mL and CCI [redacted] µg•h/mL, which provides approximately CCI [redacted] and CCI [redacted] fold safety margins (based on free concentrations), respectively. The maximum recommended starting dose based on HED approach with safety factor of 10 is CCI [redacted] mg. Given the absence of target from healthy participants, absence of off-target pharmacology and high safety margin based on pre-clinical toxicology studies, the proposed starting dose of 150 mg is expected to be safe.

Dose escalation is aimed to occur in incremental increases of ≤½ log (ie, up to approximately 3.3-fold) based on predicted exposures. The margins for the highest proposed single dose (6000 mg) established on the free exposures in rats are projected to be approximately CCI [redacted] fold for C_{max} and CCI [redacted] fold for AUC_{24} which are within the NOAEL exposure.

The nominal doses, projected PK exposure parameters and safety margins of PF-07817883 relative to PK stopping limits at the planned doses in SAD are listed in Table 15. Doses presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data. The projected exposures (adjusted based on observed PK) at the modified doses will not exceed the PK stopping limits (Section 6.6.1).

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 15. Predicted Human Exposure and Safety Margins of PF-07817883 Relative to Exposure Limits at Planned Dose Levels in SAD

Dose Levels	Dose (mg)	C_{max} (µg/mL)	AUC_{24} (h*µg/mL)	Predicted $f_{u,human}$ at C_{max} [c]	Predicted $f_{u,human}$ at C_{av} [c]	C_{max} [a,c] safety margin	AUC_{24} [b,c] safety margin
D1	CCI						
D2							
D3							
D4							
D5							
D6							

a. C_{max} safety margin = free $C_{max,ss}$ of PF-07817883 on Day 11 at NOAEL (CCI mg/kg/day) divided by projected free C_{max} in humans.
b. AUC_{24} safety margin = free $AUC_{24,ss}$ of PF-07817883 on Day 11 at NOAEL (CCI mg/kg/day) divided by projected free AUC_{24} in humans.
c. Linear regression model predicted fraction unbound in human; Free fraction (f_u) in Rat=CCI NOAEL exposures (Total) =CCI µg/mL for C_{max} and CCI µg•h/mL for AUC_{24}.

The starting dose in MAD cohort is planned at CCI mg BID; however, the starting dose in MAD may be adjusted based on available PK and safety data from the SAD cohorts. Based on the current human PK predictions, a dose of approximately CCI mg BID would provide the C_{min} consistently above C_{eff} in most participants and thus CCI mg BID is considered within the efficacious dose range. Since the target is not expressed in healthy participants and lack of evidence of off-target pharmacology (>100 µM), a dose that is expected to be in efficacious dose range is proposed as a starting dose in MAD.

Based on the predicted steady-state exposures ($C_{max,ss}$ and $AUC_{24,ss}$), CCI mg BID is expected to provide margins of approximately CCI-fold for $C_{max,ss}$ and CCI-fold for $AUC_{24,ss}$ relative to the free exposure in rats on Day 11 at the NOAEL. All dose levels listed are nominal since doses will be driven by exposure. Dose escalation is aimed to occur in incremental increases of ≤½ log (ie, up to approximately 3.3-fold) based on predicted exposures.

Due to the uncertainties in the in vitro potencies and PK parameters scaling and anticipated interpatient variability, the current intent of the development program is to explore dosing regimens resulting in a multiple of this C_{min} target. Highest daily dose of PF-07817883 is expected to be 6000 mg/day (ie, 3000 mg BID), which is expected to provide margins of approximately CCI fold for $C_{max,ss}$ and CCI fold for $AUC_{24,ss}$ relative to the free exposure in rats on Day 11 at the NOAEL.

The nominal dosing regimen, projected PK exposure parameters and safety margins of PF-07817883 relative to PK stopping limits at the planned doses in MAD are listed in Table 16.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 16. Predicted Human Exposure and Safety Margins of PF-07817883 Relative to Exposure Limits at Planned Dose Levels in MAD

Dose Regimens	Dose (mg) and Frequency	$C_{max,ss}$ (µg/mL)	$AUC_{tau,ss}$ (h*µg/mL)	Predicted $f_{u,human}$ at C_{max} [c]	Predicted $f_{u,human}$ at C_{av} [c]	C_{max} [a,c] safety margin	AUC_{24} [b,c] safety margin
DR1	CCI						
DR2							
DR3							
DR4							

a. $C_{max,ss}$ safety margin = free $C_{max,ss}$ of PF-07817883 on Day 11 at NOAEL (CCI mg/kg/day) divided by projected free $C_{max,ss}$ in humans.
b. $AUC_{24,ss}$ safety margin = free $AUC_{24,ss}$ of PF-07817883 on Day 11 at NOAEL (CCI mg/kg/day) divided by projected free $AUC_{24,ss}$ (ie, 2×$AUC_{tau,ss}$ for BID) in humans.
c. Linear regression model predicted fraction unbound in human used for free AUC_{24} and free C_{max} calculation; Free fraction (fu) in Rat=CCI, NOAEL exposures (Total) =CCI µg/mL for $C_{max,ss}$ and CCI µg•h/mL for $AUC_{24,ss}$.

All the doses in SAD or MAD cohorts except starting dose of 150 mg in SAD cohort are nominal and may be adjusted, as the study progresses depending upon emerging PK, PD, safety, and tolerability data. Other intermediate doses or lower doses or repeat doses may be administered instead of the planned doses, or changes in dosing frequency or titration schemes may be proposed for MAD cohorts if safety/tolerability issues become apparent, if evidence of nonlinear PK dictates the need to escalate more slowly, or if subsequent doses are predicted to result in exposures that exceed the target limits. However, the projected exposure for the modified doses or additional cohorts following either single dose or multiple dose administration will not exceed PK stopping limit.

The dosing regimen to be evaluated in optional Chinese and Japanese cohorts will be equal to or lower than the safe and tolerated dosing regimen in Western healthy adult participants in MAD cohorts. Similarly, the dose of PF-07817883 to be evaluated in PART-3: RBA/FE, PART-4: ME and PART-5: DDI will be the dose which will be projected to provide the exposure equal to or lower than the exposure already observed in SAD or MAD cohorts at safe and tolerated doses.

Given PF-07817883 has a potential of CYP3A induction, midazolam dose of 5 mg was selected to ensure sufficient exposure in the presence of most potent inducers.

4.3.2. Justification of Dose for PART-3:RBA/FE

In PART-3:RBA/FE, the dose of PF-07817883 to be evaluated is 600 mg. Based on preliminary population PK model using emerging PK data from PART-1 and PART-2, a dose of CCI mg BID is expected to achieve EC_{90} at C_{trough} in more than 90% of the participants. Therefore, the highest dose being evaluated in efficacy study is CCI mg BID.

PF-07817883 was safe and well tolerated up to CCI mg in PART-1 when administered as suspension in fasted state. The exposure of tablets (Formulation 1 and 2) is expected to be

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

lower than the suspension. CCI [redacted]. Thus, a dose of PF-07817883 CCI mg in PART-3 is expected to be safe.

4.3.3. Justification of Dose for PART-6:SE (Protocol Amendment 2, 31 January 2023)

In PART-6, the total dose planned for PF-07817883 is 6000 mg administered as 2 split doses of 3000 mg at 0 and 1h.

Based on preliminary data from PART-1 and PART-2 of this study, doses of PF-07817883 CCI [redacted]

The dose of moxifloxacin to be used in this study is 400 mg. This dose is the typical dose of moxifloxacin used as a positive control.

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, including all parts, 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. Use of a

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants, male or female, 18 to 60 years of age, inclusive, at the time of signing the ICD. Only Male participants will be included in PART-4.

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

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, PE, laboratory tests, and standard 12-lead ECG.

Other Inclusion Criteria:

3. BMI of 17.5 to 30.5 kg/m2; and a total body weight >50 kg (110 lb). A lower entry weight of 45 kg may be considered if the total blood volume collection for the study does NOT exceed 360 mL over an 8-week period. If the blood volume collected is expected to be >360 mL and <550 mL over an 8-week period, then the lower weight limit at screening should be 50 kg.

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

5. For optional Japanese cohort or PART-5 only: Japanese participants who have 4 Japanese biologic grandparents who were born in Japan.

6. For optional Chinese cohort or PART-5 only: Chinese participants who were born in mainland China and both parents are of the Chinese descent.

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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, HBcAb, or HCVAb. Hepatitis B vaccination is allowed.

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic 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. **PART-5 Only:** Clinically relevant abnormalities requiring treatment (eg, acute myocardial infarction, unstable ischemic conditions, evidence of ventricular dysfunction, serious tachy or brady arrhythmias) or indicating serious underlying heart disease (eg, prolonged PR interval, cardiomyopathy, heart failure greater than NYHA 1, underlying structural heart disease, Wolff Parkinson-White syndrome).

5. **PART-5 Only:** History of acute narrow-angle glaucoma, untreated open-angle glaucoma, sleep apnea, severe respiratory insufficiency, myasthenia gravis.

Prior/Concomitant Therapy:

6. Use of prescription or nonprescription drugs and dietary and herbal supplements within 28 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.9 for additional details).

7. Current use of any prohibited concomitant medication(s) or participant unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.9.

8. 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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Prior/Concurrent Clinical Study Experience:

9. 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:

10. A positive urine drug test.

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

12. Renal impairment as defined by an eGFR in adults, of <75 mL/min. Based upon participant age at screening, eGFR or eCrCl is calculated using the recommended formulas in Section 10.7.2 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events.

13. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms or QRS interval >120 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 the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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

    - AST **or** ALT level ≥1.5 × 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.

Other Exclusion Criteria:

15. 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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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).

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

17. Unwilling or unable to comply with the criteria in the Section 5.3 of this protocol.

18. Use of tobacco or nicotine containing products in excess of the equivalents of 5 cigarettes per day or 2 chews of tobacco per day.

19. **PART-5 Only**: History of sensitivity reactions to midazolam, or any of the formulation components.

20. **PART-6 Only:** Self-reported history or risk factors for QT prolongation or torsades de pointes (eg, organic heart disease, congestive heart failure, hypokalemia, hypomagnesaemia, congenital long QT syndrome, myocardial ischemia or infarction), congenital deafness, family history of sudden death, and family history of long QT syndrome.

21. 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.

22. Pregnant or breastfeeding women.

23. **PART-6 Only:** Participants who according to the product label for moxifloxacin, would be at increased risk if dosed with moxifloxacin (ie, including but not limited to participants with history of myasthenia gravis, tendinitis/tendon rupture).

24. **PART-6 Only:** History of hypersensitivity, allergy, severe adverse drug reaction or intolerance to quinolone antibiotics, including moxifloxacin.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use acceptable 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 safety laboratory evaluations and at least 10 hours before morning doses on PK days.
- PART-1, PART-3, PART-4, PART-6 and on PK days in PART-2 and PART-5 (**if dosed under fasted condition**):
  - Water is permitted until 1 hour prior to study intervention administration at 0h on PK days. Water may be consumed without restriction beginning 1 hour after dosing at 0h on PK days except PART-6 in which the intake of water remains restricted until 1h after 2nd split dosing. Water consumption is not restricted on evening dose(s) on PK days and on all doses of non-PK days.
  - No food will be allowed for approximately 4 hours post-dose (or post-split-doses in PART-6) in PART-1, PART-3, PART-6 and after the morning dose on PK days (Days 1, 5, 10) in PART-2 and PART-5. For all other doses in PART-2 and PART-5, no food will be allowed approximately 2 hours before and after dosing.
- Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices (see below) may be consumed with meals and the evening snack.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

- **PART-6 Only:** Participants will be restricted to consuming ambient temperature or warm drinks from Day 1, (prior to baseline ECG measurements), until final ECG measurements have been collected in each study period.

- Lunch will be provided approximately 4 hours after morning dosing.

- Dinner will be provided approximately 9 to 10 hours after morning 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 with the exception of dosing days where a high-fat/high-calorie meal will be given prior to study intervention. The daily caloric intake per participant should not exceed approximately 3200 kcal.

If dosed under standard meal condition in PART-1 or PART-3 or PART-4:

Following an overnight fast of at least 10 hours, participants should start a standard breakfast approximately 30 minutes prior to the administration of the study intervention. The breakfast will be consumed over approximately 20 minutes with study intervention administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to eat the full standard meal. If participants are unable to complete the entire meal, the approximate portion of the meal consumed will be documented. No food will be allowed for at least 4 hours post-dose.

- Water can be allowed as desired except for 1 hour after study intervention administration. There are no water restrictions prior to dosing for participants dosed under fed conditions.

If dosed under high-fat meal condition in PART-1 or PART-3 or PART-4:

- Following an overnight fast of at least 10 hours, participants should start a high-fat/high-calorie breakfast approximately 30 minutes prior to administration of the study intervention. The breakfast will be consumed over approximately 20 minutes with study intervention administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to eat the full meal. If participants are unable to complete the entire meal, the approximate portion of the meal consumed will be documented. No food will be allowed for at least 4 hours post-dose.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

- The breakfast will be a high-calorie/high-fat test meal. The test meal should derive approximately 150, 250 and 500-600 calories from protein, carbohydrate and fat, respectively. The following breakfast a representative example of a high-fat, high-calorie meal: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 fluid ounces (240 mL) of whole milk.

- Water can be allowed as desired except for 1 hour after study intervention administration. There are no water restrictions prior to dosing for participants dosed under fed conditions.

If dosed under standard meal condition in PART-2 and PART-5:

Morning dosing condition:

Following an overnight fast of at least 10 hours, participants should start a standard breakfast approximately 30 minutes prior to the morning administration of the study intervention. The breakfast will be consumed over approximately 20 minutes with study intervention administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to eat the full standard breakfast. If participants are unable to complete the entire breakfast on PK profile assessment days (Days 1, 5 and 10), the approximate portion of the breakfast consumed will be documented. On non-PK days, it is not required to document the approximate portion of food consumed. No food will be allowed for at least 4 hours post-dose on PK days.

Water can be allowed as desired except for 1 hour after study intervention administration on PK days. There are no water restrictions on non-PK days neither prior to dosing for participants dosed under fed conditions.

Evening dosing condition:

A snack consisting of at least 400 kcal will be provided approximately 20 minutes before dosing in the evening. The snacks will be consumed over approximately 10 minutes with study intervention administered within approximately 10 minutes after completion of the snack. Participants will be encouraged to eat the full snack. There is no food restrictions on evening dose(s).

There are no water restrictions on evening dose(s) on PK days and on non-PK days.

5.3.2.1. Dietary Fiber Supplementation (PART-1 and PART-4 only)

To help assure regularity in bowel movements, nutritional composition should include high fiber content except when required by the study design (eg, high-fat diet for FE). This may include consumption of fiber capsules, at a frequency dictated by investigator, starting with the evening meal (ie, approximately 8 or 9 hours post dose) on Day 1, for duration of inpatient stay to ensure at least 1 bowel movement per day.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

If an individual participant has not experienced a bowel movement in the first 24 hours after dosing water intake should be increased and prune juice should be offered on Day 2.

Despite these measures, if bowel movement does not occur regularly (ie, at least once daily bowel movement), consideration should be given to administration of mild laxative/stool softener (eg, milk of magnesia or docusate), at investigator's discretion.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. 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, respiratory rate and ECG measurements) for first 4 hours after morning dose, and may be required to follow meals and dietary restrictions as specified in Section 5.3.2.

- **PART-1 and PART-6 only:** Participants will be confined to the procedure room for the first 4 hours after last PF-07817883/placebo or moxifloxacin/placebo (in PART-6 only) dosing on Day 1 during continuous cardiac monitoring, except to use the bathroom. After this, if the equipment setup allows, participants may be ambulatory during the ECG monitoring period, but should not engage in strenuous activities. If equipment does not allow ambulation, appropriate accommodations will be made by the investigator site to facilitate continuous monitoring (eg, bedside urinals should be provided to accommodate participants' excretory needs).

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 at Investigator's discretion.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and non IMPs, 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, placebo, moxifloxacin or midazolam.

6.1. Study Intervention(s) Administered

Study Intervention(s)				
Intervention Name	PF-07817883	Placebo	Midazolam	Moxifloxacin
Arm Name (group of participants receiving a specific treatment or no treatment)	PART-1 through PART-5	PART-1 and PART-2	PART-5	PART-6
Type	Drug	Drug	Drug	Drug
Dose Formulation	Suspension/Solution or solid oral formulation (eg, tablet)	Suspension/Solution or solid oral formulation (eg, tablet)	Solution	Tablet
Unit Dose Strength(s)	Planned oral suspension/solution doses ranging from 150 mg to 6000 mg. Planned nominal solid oral formulation strength 100 - 400 mg pending final formulation development and dose.	0 mg	As available locally	As available locally.
Dosage Level(s)	Planned oral suspension/solution doses ranging from 150 mg to 6000 mg. Planned nominal solid oral formulation strength 100 - 400 mg pending final formulation development and dose.	0 mg	5 mg SD	400 mg
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Probe substrate	Active control
IMP or NIMP/AxMP	IMP	IMP	NIMP/AxMP	NIMP/AxMP
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.	Provided locally by the CRU.	Provided locally by the CRU.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Study Intervention(s)				
Packaging and Labeling	Materials (API and components) for extemporaneous prep of oral suspensions will be provided in bulk. Tablets will be provided in bulk. CRU staff will prepare individual doses for administration. Individual dose containers will be labeled by site staff per country requirement.	Materials (API and components) for extemporaneous prep of oral suspensions will be provided in bulk. Solid oral formulation will be provided in bulk. CRU staff will prepare individual doses for administration. Individual dose containers will be labeled by site staff per country requirement.	CRU will procure commercially labeled materials.	CRU will procure commercially labeled materials.
Current/Former Name(s) or Alias(es)	PF-07817883	Placebo	As available locally	As available locally.

PF-07817883 and placebo will be provided by Pfizer as bulk powders for extemporaneous preparation of oral suspensions at the CRU.

PF-07817883 and placebo will be presented to the participants in individual dosing containers.

In addition, PF-07817883 and matching placebo may also be supplied as tablets. If provided, tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

Midazolam and moxifloxacin will be supplied by the CRU.

6.1.1. Administration

6.1.1.1. PART-1:SAD

If dosed under fasted condition, participants will receive PF-07817883/placebo at approximately 08:00 hours (±2 hours) per the SoA following an overnight fast of at least 10h.

Investigator site personnel will administer with ambient temperature water to a total volume of approximately 240 mL. Study intervention will be administered according to the EDR for oral suspension.

If dosed under fed condition (standard meal or high-fat high-calorie meal), the PF-07817883/placebo (placebo for PART-1 only) should be administered approximately 10 minutes after finishing the meal/snack (refer Section 5.3.2 for further details).

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

6.1.1.2. PART-2:MAD

If dosed under fasted condition, participants will receive PF-07817883/placebo at approximately 08:00 hours (plus or minus 2 hours) per the SoA following an overnight fast of at least 10 hours. At least 2h of fast is required for evening dosing.

Investigator site personnel will administer with ambient temperature water to a total volume of approximately 240 mL. Study intervention will be administered according to the EDR for oral suspension.

If dosed under fed condition (meal/snack), the PF-07817883/placebo should be administered approximately 10 minutes after finishing the meal/snack (refer Section 5.3.2 for further details).

6.1.1.3. PART-3: RBA/FE

If dosed under fasted condition, participants will receive PF-07817883 at approximately 08:00 hours (±2 hours) per the SoA following an overnight fast of at least 10h. Participants will swallow PF-07817883 oral formulation(s) whole (if administered as solid dose units eg, tablet) and will not chew prior to swallowing.

Investigator site personnel will administer with ambient temperature water to a total volume of approximately 240 mL. Study intervention will be administered according to the EDR for oral suspension.

If dosed under fed condition (standard meal or high-fat high-calorie meal), the PF-07817883 should be administered approximately 10 minutes after finishing the meal/snack (refer Section 5.3.2 for further details).

6.1.1.4. PART-4: ME

Participants will receive PF-07817883 at approximately 08:00 hours (±2 hours) per the SoA following an overnight fast of at least 10h.

Investigator site personnel will administer PF-07817883 oral suspension with ambient temperature water to a total volume of approximately 240 mL. PF-07817883 oral suspension will be administered according to the EDR for oral suspension.

If dosed under fed condition (meal/snack), the PF-07817883 should be administered approximately 10 minutes after finishing the meal/snack (refer Section 5.3.2 for further details).

6.1.1.5. PART-5: DDI

In this part, for Treatment A (midazolam), participants will receive oral solution of midazolam at approximately 08:00 hours (±2 hours) per the SoA following an overnight fast of at least 10h. For Treatment B, if dosed under fasted condition, participants will receive PF-07817883 at approximately 08:00 hours (±2 hours) per the SoA following an overnight

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

fast of at least 10 hours. At least 2h of fast is required for evening dosing for BID dosing regimen. When dosed together with midazolam, both should be administered within 5 min of each other.

Investigator site personnel will administer with ambient temperature water to a total volume of approximately 240 mL. PF-07817883 will be administered according to the EDR for oral suspension.

If dosed under fed condition (meal/snack), the PF-07817883 should be administered approximately 10 minutes after finishing the meal/snack (refer Section 5.3.2 for further details).

6.1.1.6. PART-6: SE

In this part, following an overnight fast of at least 10 hours, for each period, participants will receive split administrations (2 doses) of PF-07817883 or placebo at short intervals (within approximately 1 h of the previous dose) or a single dose of moxifloxacin at 0h and placebo at 1h.

To participants randomized to receive PF-07817883 or placebo the first split-dose of PF-07817883 or placebo may be administered at 08:00 hours (±2 hours). The second split dose will be administered at approximately 1h after the first dose. The participants randomized to moxifloxacin would receive moxifloxacin tablet at 08:00 hours and placebo suspension at 1h. In all subsequent treatment periods, the timing of dose administration for a given participant must be matched to that of the first period (±15 minutes). Administration of study interventions will be carried out according to the conditions described in the Lifestyle Considerations section of this protocol. Investigator site personnel will administer study interventions during each period with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study interventions whole, and will not manipulate or chew the study interventions prior to swallowing.

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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 procedures.

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

6. See the EDR for storage conditions of the study intervention once prepared.

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

8. 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.

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

PF-07817883 and placebo oral dosing suspensions will be prepared in the CRU by 2 operators, 1 of whom is a pharmacist. Details of dose preparation will be given in a

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

separate EDR. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

PF-07817883 and placebo tablets, if used, will be dispensed 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.

Midazolam will be administered to the participant in an unblinded (open-label) fashion. Midazolam solution will be dispensed 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 solution will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

PF-07817883 and placebo will be prepared by qualified unblinded site personnel as per local procedure. Blinded study intervention will be administered in a blinded fashion to the participant. Blinding procedures do not apply to PART-3, PART-4, and PART-5 of this study because it will be conducted as open-label.

Moxifloxacin 400 mg tablets will be prepared in an open-label manner at the NH 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, practitioner, or pharmacist). Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator 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 a double-blind, study with optional open-label parts.

Blinding procedures do not apply to PART-3, PART-4, and PART-5 of this study because it will be conducted as open-label. Where the design is open-label, the investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention in PART-1, PART-2 and PART-6 (except moxifloxacin) only.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention in PART-1, PART-2 and PART-6 (except moxifloxacin) only.

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

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

CRU Pharmacy staff responsible for preparing all study intervention will be unblinded. CRU site staff responsible for providing technical system support to the Pharmacy staff and supporting blinded laboratory data processes will be unblinded. These site staff providing system support are not involved in any data collection or clinic floor activities.

6.4.3. Blinding of the Sponsor

Limited number of sponsor staff will be unblinded to participants' assigned study intervention in PART-1, PART-2 and PART-6 (except moxifloxacin) of the study for the purpose of, including but not limited to, unblinded review, dose escalation, regulatory interactions, drug development decisions.

6.4.4. Breaking the Blind

The method for breaking the blind in this study will be manual. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data; and provide information necessary to potentially alter the dose escalation sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

the study has been completed. Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.6. Dose Modification

Progression to the next dose in PART-1 will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data. Each dose escalation will be based on review of the safety data up to a minimum of 48 hours post-dose plus PK assessments up to 6 hours post-dose, in at least 3 actively treated participants and at least 1 placebo-treated participant dosed in the previous dose level.

Progression to the next dose in PART-2 will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data. Each dose escalation will be based on review of the safety data up to a minimum of 6 days plus PK assessments up to 6 hours post-dose on Day 5, in at least 3 actively treated participants and at least 1 placebo-treated participant dosed in the previous dose level.

Dose for PART-3, PART-4, and PART-5 will be determined based on emerging PK and safety data (Section 4.3).

6.6.1. Dose Escalation and Stopping Rules

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not overrule the investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the study intervention.

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

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

- If 2 or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant ECG abnormalities, indicating dose-limiting intolerance.

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

- Dosing will be paused if 2 or more participants at a given dose level (but not participants receiving placebo) experience a moderate nonserious AE within SMQ of peripheral neuropathy or rhabdomyolysis/myopathy, considered as, at least, possibly related to study intervention administration. The AEs will be evaluated by the sponsor's unblinded study team. If the events are determined to be dose-limiting, doses in subsequent dosing periods may be modified downwards, or dose-escalation may be terminated. If it is determined that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented.

- Dosing will be paused for any SAE that occurs in a participant receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug-related by the PI and sponsor. If the SAE is determined to be either drug-related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.

- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.

- Other findings that, at the discretion of the study team and investigator, indicate that dose escalation should be halted.

- If, at any dose level, the average exposure reaches or exceeds the PK stopping limits, total plasma AUC_{24} ($AUC_{24} = 2 \times AUC_{tau}$ for BID in PART-2) and C_{max} of CCI µg•h/mL and CCI µg/mL.

- If, based on the observed data, the group mean C_{max} or AUC (based on total plasma concentration) of the next planned dose is projected to exceed the escalation limits, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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

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 at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.
5. Obtain a blood sample for PK analysis within 3 days 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 28 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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.

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. ECG Changes

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

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

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.

7.1.2. Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum CK, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants in a given period in PART-1, PART-3, PART-5, and PART-6 and in treatment arm in PART-2 and PART-4 are noted to have *2 consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.1.3. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Study treatment may continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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;

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

- 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.

7.4. Stopping Criteria for PART-6:SE

7.4.1. Stopping Criteria for Sentinel Dosing:

- Dosing will be paused for any SAE considered treatment related or unknown by the PI, until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug-related by the PI and sponsor.

- At the discretion of PI, if any participant receiving PF-07817883 or placebo develops clinically significant laboratory, or vital sign abnormalities, or ECG abnormalities, the dosing of additional participants may also be paused until causality is fully assessed by the PI and sponsor. Laboratory, vital sign, or ECG abnormalities assessed as severe (as defined in assessment of severity in Section 10.3.3) would be considered clinically significant, warranting stopping of further dosing . Dosing may resume if the event is determined to be not drug-related by the PI and sponsor.

7.4.2. Stopping Criteria Following Evaluation of Safety Data from the First 6 Participants (Periods 1 to 3) in PART-6:SE

- If 50% or more of the participants receiving active drug but not receiving placebo develop similar clinically significant laboratory, or vital sign abnormalities, in the same organ class, indicating dose-limiting intolerance.

- If 2 or more of the participants receiving active drug (but not participants receiving placebo) develop similar clinically significant ECG abnormalities, indicating dose-limiting intolerance.

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

- Dosing will be paused if 2 or more participants (but not participants receiving placebo) experience a moderate nonserious AE within SMQ of peripheral neuropathy or rhabdomyolysis/myopathy, considered as, at least, possibly related to study intervention administration. The AEs will be evaluated by the sponsor's unblinded study team. If the events are determined to be dose limiting, doses in subsequent dosing periods may be modified downwards, or dose escalation may be terminated. If

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

it is determined that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented.

- Dosing will be paused for any SAE that occurs in a participant receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug related by the PI and sponsor. If the SAE is determined to be either drug related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.

- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.

- Other findings that, at the discretion of the study team and investigator, indicate that dosing of additional participants should be halted.

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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 be used without repeat collection, as appropriate.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that 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.

Safety/laboratory/analyte results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (PR 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 up to 390, 235, 210, 160, 360 mL and 485 mL in PART-1, PART-2, PART-3, PART-4, PART-5 and PART-6, respectively. 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 Prior 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 as well as blood donation within 60 days prior to enrollment. If the participants are discharged between the periods in PART-1:SAD, PART-3:RBA/FE and PART-5:DDI, medical history may be updated.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

8.1.1.2. Demographics

Participants' race, ethnicity, age, gender, height and weight will be recorded at screening . If discharged at investigator's discretion, the demographics will not be recorded in subsequent periods.

8.2. Efficacy Assessments

No efficacy assessment is planned 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. Physical Examinations

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

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

The limited targeted neuromuscular exam as per SoA will include the assessment of the motor system (tone and strength), reflexes, coordination and gait.

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.

PE findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward PE 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. Vital Signs

8.3.2.1. 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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

(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 PR is acceptable; however, when done manually, PR 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 PR should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and PR 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.

8.3.2.2. Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes of rest in a supine position by observing and counting the respirations of the participant for 30 seconds and multiplying by 2. When BP is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before BP measurement.

8.3.3. Electrocardiograms

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

For PART-1, PART-2, and PART-6 only:

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected before dose administration on Day 1 in each period in PART-1 and PART-6 and on Day 1 in PART-2 will serve as each participant's time-controlled baseline QTcF value.

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) the mean value from the triplicate measurements for any post-dose 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 a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

For PART-3, PART-4 and PART-5 only:

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.

For all parts:

If a) a post-dose 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 8.

8.3.3.1. Continuous Cardiac Monitoring by Telemetry (PART-1 and PART-6 only)

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

Telemetry should be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the investigator site, or verifiable arrhythmia quantification is required. To establish a baseline, telemetry should be recorded for at least 2 hours between admission and before dosing in Period 1 only while awake. This may be done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the participant is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.

8.3.4. 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 6 for suggested actions and follow-up assessments in the event of potential DILI.

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

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.

8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Not applicable.

8.3.5. COVID-19 Specific Assessments

Participants will undergo COVID-19 related measures as per local CRU procedures.

8.3.6. Pregnancy Testing

A 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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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

8.4. 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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

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

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 7 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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.

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

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

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

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

8.5. PK

8.5.1. Plasma for Analysis of PF-07817883 PK, Total Drug-Related Material Measurement, and Metabolic Profiling

Blood samples of approximately 3 mL, to provide approximately 1 mL of plasma, will be collected for measurement of plasma concentrations of PF-07817883 as specified in the SoA. In PART-2: MAD portion of the study conducted at NH CRU only, exploratory microsampling PK blood samples for the measurement of PF-07817883 concentrations may be collected. Total blood volume for exploratory microsampling PK will not exceed 0.1 mL at each time point specified in the SoA. When an exploratory microsampling PK blood sample is collected, a 0.1 mL portion of the PK blood sample will also be collected and used to determine the blood to plasma ratio of PF-07817883. In PART-1 (at selected doses at which urine and feces are collected) and PART-4 of the study, blood samples of approximately 10 mL may be collected for the measurement of drug-related materials using ^{19}F-NMR and/or metabolic profiling as specified in the SoA. Instructions for the collection

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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 collected for analyses of PF-07817883 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 the measurement of PK biomarkers or for other internal exploratory purposes.

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

Samples collected for measurement of plasma concentrations of PF-07817883 will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples collected for exploratory PK may be analyzed with either validated or qualified methods. This exploratory data will not be included in the clinical study report. Potential metabolites may be analyzed with either validated or exploratory methods.

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

Drug concentration information that would unblind the study will not be reported to investigator sites or blinded personnel until the respective cohort of study has been unblinded.

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

8.5.2. Plasma for PK Analysis of Midazolam (PART-5: DDI only)

Blood samples of approximately 4 mL, to provide approximately 1.5 mL plasma, will be collected for measurement of plasma concentrations of midazolam 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 midazolam and its metabolites (if necessary). Samples may also be used to evaluate safety aspects related to concerns arising during or after the study and/or evaluation of the bioanalytical method, or for the measurement of PK biomarkers or for other internal exploratory purposes.

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

Samples collected for measurement of plasma concentrations of midazolam will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples collected for exploratory PK may be analyzed with either validated or qualified methods. This exploratory data will not be included in the clinical study report. Potential metabolites may be analyzed with either validated or exploratory methods.

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

Drug concentration information that would unblind the study will not be reported to investigator sites or blinded personnel until the respective cohort of study has been unblinded.

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5.3. Plasma for PK Analysis of Moxifloxacin (PART-6: SE only)

Blood samples of approximately 4 mL, to provide approximately 1.5 mL plasma, will be collected for measurement of plasma concentrations of moxifloxacin 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 explore the PK of moxifloxacin. Samples collected for this exploratory PK may be analyzed with either validated or qualified methods. Samples may also be used to evaluate safety aspects related to concerns arising during or after the study and/or evaluation of the bioanalytical method, or for the measurement of PK biomarkers or for other internal exploratory purposes. This exploratory data will not be included in the CSR.

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

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

8.5.4. Plasma for the Measurement of PK Biomarkers (PART-2)

Blood samples of approximately 4 mL, to provide approximately 1.5 mL of plasma, will be collected for measurement of plasma concentrations of endogenous PK biomarkers, such as cholesterol, hydroxycholesterol, CP-I, CP-III, IBC etc, 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.

Sample collected for PK biomarkers may also be used to evaluate safety or efficacy or PK aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for the measurement of PK biomarkers or for other internal exploratory purposes.

8.5.5. Urine PK (PART-2 only)

Urine samples will be collected for an interval as specified in the SoA and mixed thoroughly and the total volume will be measured and recorded on the CRF. An aliquot of approximately 5 mL will be collected for the measurement of urine concentrations of PF-07817883. 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 start and end of each collection interval will be recorded.

The urine blank (approximately 5 mL) for PK will be obtained prior to dosing.

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

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

Drug concentration information that would unblind the study will not be reported to investigator sites or blinded personnel until the respective cohort of the study has been unblinded.

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

As part of understanding the PK of the study drug, samples may be used for exploratory purposes, metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the CSR.

8.5.6. Urine and Feces for Measurement of Drug-Related Material and Metabolic Profiling (PART-1 and PART-4)

Urine will be collected for determination of total drug-related material and metabolite profiling as specified in the SoA. The participants will force void before oral dosing. Prior to dosing on Day 1 (within 24 hours), each participant must empty his or her urinary bladder; an aliquot from this urine will serve as the "urine blank". The details regarding the collection, processing, storage and shipping of the urine samples will be provided in the lab manual and supporting documentation.

Feces will be collected for determination of total drug-related material by ^{19}F-NMR spectroscopy and metabolite profiling as specified in the SoA. A pre-dose fecal sample within 48 hours prior to dosing should be collected.

Details of the collection of aliquots, volume, processing, storage and shipping of the urine and feces samples will be provided in the lab manual and supporting documentation. The actual date and time (24-hour clock time) of each sample will be recorded.

At the discretion of the sponsor, one or more assessments on urine and feces may not be conducted if deemed unnecessary by the sponsor.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

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

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

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

8.7. Biomarkers

8.7.1. Specified Gene Expression (RNA) Research

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

8.7.2. Specified Protein Research

Specified protein research is not included in this study.

8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.4. Retained Research Samples for Biomarkers

Not applicable.

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. Taste Assessment of PF-07817883 (PART-3 only)

The sensory attributes of PF-07817883 will be evaluated by the participant using a Taste Assessment Questionnaire (Appendix 9). When suspension is to be administered, each participant will complete the Taste Assessment Survey immediately following dosing (within 1 min) *plus* at 5, 10, and 20 minutes post oral administration of PF-07817883 oral suspension. For solid oral formulations, the taste assessment will be completed immediately after dosing (within 5 min) and at 1, 2, 4 and 8h post-dose as specified in SoA.

All efforts will be made to initiate the questionnaire at the nominal time relative to 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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention for the given part of the study.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK Concentration Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported for the given part of the study.
PK Parameter Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest are reported for the given part of the study.

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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

9.3.1. General Considerations

The data from each part of the study will be analyzed and reported separately in a single CSR issued at the end of this study.

9.3.2. Primary Endpoint(s) Analysis

The primary endpoints in PART-1, PART-2 and PART-6 are related to safety/tolerability with analyses as described in Section 9.3.5.

The primary endpoints in PART-3 and PART-5 are the plasma PK endpoints whose analyses are described in Sections 9.3.3.1 and 9.3.3.2.

The primary endpoints in PART-4 are percent recovery and cumulative recovery of drug-related material in urine and feces determined based on total administered dose. Percent recovery of drug-related material in urine and feces will be determined based on total administered dose. The total recovery of drug-related material in urine and feces and their combination will be listed and summarized.

9.3.3. Secondary Endpoint(s) Analysis

The secondary endpoints in PART-1, PART-2, PART-4 and PART-6 as well as the primary endpoints in PART-3 and PART-5 related to PK are described herein.

9.3.3.1. PK Analysis

9.3.3.1.1. Derivation of PK Parameters

Plasma PK parameters for PF-07817883 will be derived (if data permit) from the concentration-time data using standard noncompartmental methods following a single oral dose (Table 17) and multiple oral doses (Table 18). Urine PF-07817883 PK parameters are described in Table 18. 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 17. Plasma PF-07817883 PK Parameters for PART-1: SAD, PART-3: RBA/FE, PART-4: ME and PART-6: SE, Midazolam PK Parameters in PART-5: DDI, and Moxifloxacin PK Parameters in PART-6: SE

Parameter	Part of the Study	Definition	Method of Determination
AUC_{last}[a,c]	1, 3, 4, 5, 6	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[b]	1, 3, 4, 5, 6	Area under the plasma concentration-time curve from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 17. Plasma PF-07817883 PK Parameters for PART-1: SAD, PART-3: RBA/FE, PART-4: ME and PART-6: SE, Midazolam PK Parameters in PART-5: DDI, and Moxifloxacin PK Parameters in PART-6: SE

Parameter	Part of the Study	Definition	Method of Determination
C_{max}[c]	1, 3, 4, 5, 6	Maximum plasma concentration	Observed directly from data
T_{max}[c]	1, 3, 4, 5, 6	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[b]	1, 3, 4, 5, 6	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline are used in the regression.
CL/F[b]	1, 3, 4, 5, 6	Apparent clearance	$Dose/AUC_{inf}$
V_z/F[b]	1, 3, 4, 5, 6	Apparent volume of distribution	$Dose/(AUC_{inf} \bullet k_{el})$
AUC_{last}(dn)	1	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf}(dn)[b]	1	Dose normalized AUC_{inf}	AUC_{inf}/Dose
C_{max}(dn)	1	Dose normalized C_{max}	C_{max}/Dose

a. In PART-5, Sequence 1, Day 1, 0h sample of midazolam in Period 2 will be considered as 48h PK for Period 1.

b. If data permit.

c. Only selected PK parameters to be calculated for moxifloxacin in PART-6

dn=dose normalized to a 1 mg dose.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Table 18. Plasma and Urine PF-07817883 PK Parameters for PART-2: MAD and PART-5: DDI

Parameter	Day(s)[a]	Definition	Method of Determination
Plasma			
AUC_τ	1, 5, 10	Area under the plasma concentration-time profile from time 0 to time tau (τ), the dosing interval, where τ = 12 hours	Linear/Log trapezoidal method
C_{max}	1, 5, 10	Maximum plasma concentration during the dosing interval	Observed directly from data
T_{max}	1, 5, 10	Time for C_{max}	Observed directly from data as time of first occurrence
C_{12}	5, 10	Concentration at 12h nominal time post-dose	Observed directly from data
PTR	5, 10	Peak-to-trough ratio	C_{max}/C_{min}
R_{ac}	5, 10	Observed accumulation ratio for AUC_τ	Day 5 or Day 10 AUC_τ/Day 1 AUC_τ
$R_{ac,Cmax}$	5, 10	Observed accumulation ratio for C_{max}	Day 5 or Day 10 C_{max}/Day 1 C_{max}
CL/F	5, 10	Apparent clearance	Dose/AUC_τ
$t_{½}$[b]	10	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline are used in the regression
V_z/F[b]	10	Apparent volume of distribution	Dose/(AUC_τ • k_{el})
AUC_τ(dn)	1, 5, 10	Dose normalized AUC_τ	AUC_τ/Dose
C_{max}(dn)	1, 5, 10	Dose normalized C_{max}	C_{max}/Dose
C_{av}	1, 5, 10	Average concentration	AUC_τ/12
Urine[c]			
Ae_τ	10	Amount excreted in urine as unchanged drug over the dosing interval τ	Sum of (urine volume × urine concentration) for each collection over the dosing interval
Ae_τ%	10	Percent of dose excreted in urine as unchanged drug over the dosing interval τ	100 * Ae_τ/Dose
CL_r	10	Renal clearance	Ae_τ/AUC_τ

a. Day 5 optional for PART-5.

b. If data permit.

c. Urine parameters are not applicable for PART-5.

dn=dose normalized to a 1 mg dose.

9.3.3.2. Statistical Methods for PK Data

No formal inferential statistics will be applied to the plasma PK data apart from the comparisons of formulation and FE in either PART-1 or PART-3 and the estimation of the

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

effect of steady-state PF-07817883 on the PK of midazolam in PART-5. The PK data for PF-07817883 and Midazolam (PART-5) will be reported separately.

For all parts of the study, plasma concentrations of each analyte will be listed and summarized descriptively by PK sampling time and treatment. Individual participant and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used for plasma samples. Median profiles will be presented on both linear-linear and log-linear scales.

In each part, the plasma and urine PK parameters of each analyte listed in Table 17 and Table 18 will be summarized descriptively by Treatment and/or dose.

For PART-3, natural log transformed AUC_{last}, C_{max}, and AUC_{inf} (if data permit) for PF-07817883 will be analyzed using a mixed effect model with sequence, period, and treatment included as fixed effects and participant nested within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Only the first 3 periods will be used in this analysis (ie, Fed formulations excluded).

To compare the Fed and Fasted formulations , natural log transformed AUC_{last}, C_{max}, and AUC_{inf} (if data permit) for PF-07817883 from these two formulations will be analyzed separately using a paired t-test. Resulting estimates of the mean differences (Test - Reference) and corresponding 90% CIs from the t-test will be exponentiated to provide estimates of the ratio of geometric means (Test/Reference) and 90% CIs for the ratios. Formulation Fasted is the Reference treatment and Formulation Fed is the Test treatment.

The following comparisons will be made (where applicable):

Comparison	Test	Reference
Formulation	PF-07817883 Oral Formulation 1 in Fasted state	PF-07817883 Oral Suspension in Fasted state (A)
	PF-07817883 Oral Formulation 2 in Fasted state	PF-07817883 Oral Suspension in Fasted state (A)
FE	PF-07817883 Oral Formulation 1 in Fed (high fat high-calorie meal) state	PF-07817883 Oral Formulation 1 in Fasted state
	PF-07817883 Oral Formulation 2 in Fed (high fat high-calorie meal) state	PF-07817883 Oral Formulation 2 in Fasted state

For PART-5, natural log transformed AUC_{last}, C_{max} and AUC_{inf} (if data permit) of midazolam will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant nested within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Midazolam alone is the Reference treatment whilst midazolam + PF-07817883 is the Test treatment.

If the number of Chinese or Japanese participants in PART-5 are ≥3 within a cohort, the plasma concentration and PK parameters of PF-07817883 may also be summarized separately for Chinese, Japanese and Western population.

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

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

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

9.3.5. Safety Analyses

In this study, assessment of safety and tolerability forms the primary objective for PART-1, PART-2 and PART-6. In all 6 parts of the study, all safety analyses will be performed on the ***Safety Analysis Set*** as defined in Section 9.2.

AEs, ECGs, BP, PR, continuous cardiac monitoring, and safety laboratory data, as applicable, will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR 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 PE 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 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 QT interval, HR, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time.

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

Safety QTcF Assessment

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-ms value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 ms will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 ms. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the time-matched baseline triplicate values on Day -1, or the average of the predose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship may be examined.

9.3.6. Other Analyses

9.3.6.1. Taste Assessment

If done, the data collected for taste assessment using the sponsor-provided taste questionnaire will be numerically derived by measuring length (using a scale with gradations of at least 0.1 centimeter) of the "x" marked by the participant relative to the "good trait". The taste attributes from the taste questionnaires (Appendix 9) will be listed and descriptively summarized and appropriate plots may be generated.

The summary and analysis of the taste assessments may not be reported in the CSR.

9.3.6.2. Pharmacogenomic/Biomarker Assessment

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

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, facilitating PK modeling, and/or supporting clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team.

9.5. Sample Size Determination

A total of up to 122 participants (16 in PART-1: SAD, up to 36 [with 2 cohorts and 4 optional cohorts] in PART-2: MAD, 12 in PART-3: RBA/FE cohort, 6 in PART-4: ME, up to 28 [with 2 cohorts of 14 each] in PART-5: DDI and 24 in PART-6: SE) are planned to be

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

enrolled in this study. Participants who discontinue for reasons other than safety during the study may be replaced at the discretion of the sponsor and Investigator.

9.5.1. PART-1: SAD

A sample size of 8 participants per cohort for this single, dose escalating, 3-period cross-over, with placebo substitution study (6 active, 2 placebo per dose level) has been chosen based on the need to minimize exposure of healthy participants to a new chemical entity and the requirement to provide adequate safety and toleration information and PK information at each dose level.

9.5.2. PART-2: MAD

A sample size of 6 participants per cohort, with 4 participants randomized to PF-07817883 plus 2 participants to placebo per cohort, has been selected as a compromise between the need to minimize exposure to PF-07817883 and the need to have sufficient participants randomized to provide adequate safety and toleration information and PK.

This sample size has been judged sufficient to obtain a preliminary evaluation of safety, tolerability, and PK data in these populations.

9.5.3. PART-3: RBA/FE

A sample size of 12 participants will provide adequate precision to compare the relative bioavailability of a solid oral formulation(s) of PF-07817883 relative to oral suspension, based on estimates of the within-participant standard deviations of CCI for $\log_e AUC_{last}$, CCI for $\log_e C_{max}$ and CCI for $\log_e AUC_{inf}$ using preliminary data from 150 mg, 500 mg, 1500 mg, 3000 mg and 4000 mg fasted doses in Cohorts 1 and 2 from PART-1: SAD. The expected widths of the 90% CIs with 80% coverage probability for the comparison of tablet formulation of PF-07817883 relative to oral suspension are shown in Table 19 or a range of possible effects.

Table 19. Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects for AUC_{last}, C_{max} and AUC_{inf}

Parameter	SD	Estimated Effect	Probable 90% CI	Probable CI Width
AUC_{last}		CCI		
AUC_{inf}				
C_{max}				

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

9.5.4. PART-4: ME

A sample size of approximately 6 male participants (with at least 4 completers) is chosen based on the industry standard sample size for ME studies. This sample size was not justified by any empirical data or hypothesis testing criteria.

9.5.5. PART-5: DDI

A sample size of 12 participants has been selected to provide sufficient precision to detect a 1.25-fold difference in Midazolam AUC_{inf}. A total of 14 participants will be randomized to ensure that at least 12 participants complete the study. The following table presents the width of 90% confidence interval for different estimated effects:

Table 20. Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects for AUC_{inf}

Parameter	Estimated Effect (100*Test/Reference)	90% CI*	CI Width*
AUC_{inf}	50%	40% to 62%	22%
	80%	64% to 100%	35%
	90%	72% to 112%	40%
	100%	80% to 125%	44%
	125%	100% to 156%	55%
	150%	120% to 187%	66%

* Rounded values.

These calculations are based on estimates of within-participant coefficient of variation of 26% for $\log_e AUC_{inf}$ (midazolam), as obtained from the Pfizer Clinical Pharmacology Guidance. The estimate of standard deviation of 0.256 for $\log_e AUC_{inf}$ was derived from within-participant coefficient of variation.

9.5.6. PART-6: SE

A sample size of approximately 24 participants will provide at least 87% power to demonstrate assay sensitivity for C-QTc modeling with pre-dose baseline as reported in Huang et al (2021).[12]

Additionally, a sample size of approximately 24 participants will provide at least 94% power to detect at least a 5 ms difference for QTcF between moxifloxacin and placebo at moxifloxacin T_{max} of 3 hours (to demonstrate study sensitivity) when the true difference is 10 ms. The statistical calculations were based on a 1-sided 5% paired t-test, assuming a common standard deviation of 5.35 ms for QTcF, according to the sponsor's historical data.

Garnett et al (2016)[13] reported that the "false negative" rate (the upper bound of 90% interval less than 10 ms) using C-QTc modeling approach was 2-6% in crossover design trials with up to 24 participants for a true ΔΔQTcF of 10 ms at a supratherapeutic concentration. For

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

scenarios with small mean effect size, the power to exclude 10 ms was increased with increasing sample size, and approximately 80% in crossover studies with 24 participants, when the true mean effect was 5 ms.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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 standard operating procedures 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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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 24 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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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 data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

10.1.7. Source Documents

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

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

Definition of what constitutes source data 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 data) 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. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, 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 if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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.

10.1.9. 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 CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy 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, and (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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 21. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Cystatin-C[g] and eGFR (2021 CKD-EPI)[h] CK	pH[f] Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy and culture[a]	• Urine drug screening[c] • SARS-CoV-2 RT-PCR • Pregnancy test (β-hCG)[d] • aPTT • PT • INR • Amylase • Lipase At screening only: • FSH[b] • HBsAg • HBsAb[e] • HBcAb • HCVAb • HIV

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase. Urinary culture only if deemed appropriate by the investigator.
b. For confirmation of postmenopausal status only (post-menopausal females only), at screening only.
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Serum pregnancy test required at screening. Serum or urine β–hCG for female participants of childbearing potential.
e. Can be done either automatically or only if HBcAb or HBsAg is positive, as per local practices.
f. Can be performed on dipstick or pH meter device.
g. Cystatin-C to be performed at baseline (Day -1 at time of admission), then repeated as deemed appropriate by the investigator.
h. Age-specific kidney function calculation as specified in Section 10.7.2.

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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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 on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs;

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

(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 AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

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

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

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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

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

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

Assessment of Intensity

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

- Mild: 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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

- 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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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

SAE Reporting to Pfizer Safety via the CT SAE Report Form

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

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

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

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants as described in Section 10.4.4.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

A female participant is eligible to participate if she (a) is not pregnant or breastfeeding; (b) agrees to not donate eggs (ova, oocytes) for the purpose of reproduction and (c) at least 1 of the following conditions applies:

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

  OR

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

- 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. Intrauterine device.

2. Intrauterine hormone-releasing system.

3. Bilateral tubal occlusion.

4. 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

5. Sexual Abstinence.

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

Highly Effective Methods That Have Low User Dependency (for WOCBP partners of male participants)

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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 (for WOCBP partners of male participants)

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

    - Oral + barrier*;

    - Intravaginal+ barrier*;

    - Transdermal+ barrier*.

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

    - Oral+ barrier*;

    - Injectable+ barrier*.

8. Sexual Abstinence.

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

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

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07817883 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

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

- The samples will be retained as indicated:

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

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

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede 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).

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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

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

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

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

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

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

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

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

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations[14]

2021 CKD-EPI SCr Only	**SCr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ⩽0.7	NA	$eGFR = 143 \times (SCr/0.7)^{-0.24} \times (0.9938)^{Age}$
Female	if >0.7	NA	$eGFR = 143 \times (SCr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ⩽0.9	NA	$eGFR = 142 \times (SCr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if >0.9	NA	$eGFR = 142 \times (SCr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI SCr-Scys Combined	**SCr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ⩽0.7	if ⩽0.8	$eGFR = 130 \times (SCr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ⩽0.7	if >0.8	$eGFR = 130 \times (SCr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if >0.7	if ⩽0.8	$eGFR = 130 \times (SCr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if >0.7	if >0.8	$eGFR = 130 \times (SCr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ⩽0.9	if ⩽0.8	$eGFR = 135 \times (SCr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ⩽0.9	if >0.8	$eGFR = 135 \times (SCr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if >0.9	if ⩽0.8	$eGFR = 135 \times (SCr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if >0.9	if >0.8	$eGFR = 135 \times (SCr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

CCI

[redacted]

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
Abs	absolute
ACE2	angiotensin-converting enzyme 2
ADL	activity/activities of daily living
AE	adverse event
Ae_{tau}; Ae_{τ}	amount excreted in urine as unchanged drug over the dosing interval τ/tau
Ae_{tau}%; Ae_{τ}%	percent of dose excreted in urine as unchanged drug over the dosing interval τ/tau
AESI	adverse events of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the plasma concentration-time profile from time 0 to the time 24 hours
$AUC_{24,ss}$	area under the plasma concentration-time profile from time 0 to the time 24 hours at steady-state
AUC_{inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinite time
AUC_{inf}(dn)	dose normalized AUC_{inf}
AUC_{last}	area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration
AUC_{last}(dn)	dose normalized AUC_{last}
AUC_{τ}; AUC_{tau}	area under the plasma concentration-time profile from time 0 to time tau (τ), the dosing interval
AUC_{τ}(dn); AUC_{tau}(dn)	dose normalized AUC_{τ}
AV	atrioventricular
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
β–hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BR	Brussels

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Abbreviation	Term
BUN	blood urea nitrogen
C_{12}	concentration at 12h nominal time post-dose
C_{av}	average concentration
C_{eff}	efficacious concentration
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 collaboration
CL	clearance
C_{last}	last quantifiable concentration
CL/F	apparent clearance
CL_r	renal clearance
C_{max}	maximum plasma concentration
C_{max}(dn)	dose normalized C_{max}
$C_{max,ss}$	maximum plasma concentration at steady-state
C_{min}	minimum observed concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	Coronavirus disease 2019
CP-I	Coproporphyrin I
CP-III	Coproporphyrin III
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTIS	Clinical Trial Information System
CTMS	clinical trial management system
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
dNHBE	differentiated normal human bronchial epithelial
D#	Dose#
DR#	dosing regimen#
EC	ethics committee
EC_{50}	half maximal effective concentration
EC_{90}	90% maximal effective concentration
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Abbreviation	Term
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eSAE	electronic serious adverse event
E/T	early termination
EU	European Union
EUA	Emergency Use Authorization
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FE	food effect
FIH	first-in-human
^{19}F-NMR	fluorine-19 nuclear magnetic resonance
FSH	follicle-stimulating hormone
f_u	free fraction
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HAE	human airway epithelial
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCoV-229E	Human coronavirus 229E
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HED	human equivalent dose
HIV	human immunodeficiency virus
HLM	human liver microsome
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IBC	Isobutyrylcarnitine
IC_{50}	inhibitory concentration 50%
ICD	Informed Consent Document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Abbreviation	Term
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous(ly)
KDIGO	Kidney Disease Improving Global Outcomes
k_{el}	first-order elimination rate constant
KO	knockout
LBBB	left bundle branch block
LFT	liver function test
mAB	monoclonal antibody
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR1	multidrug resistance mutation 1
ME	Metabolism and Excretion
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
M^{Pro}	main protease
MQI	medically qualified individual
NA	not applicable
NH	New Haven
NH CRU	New Haven clinical research unit
NHP	non-human primates
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
OATP	organic anion transporting polypeptides
Papp	apparent permeability coefficient
PBPK	physiology based pharmacokinetic
PD	pharmacodynamic(s)
PE	physical examination
P-gp	p-glycoprotein
PI	Primary Investigator
PK	pharmacokinetic(s)
PL	placebo
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PTR	peak-to-trough ratio
PVC	premature ventricular contraction
QTc	corrected QT interval
QTcF	corrected QT interval using Fridericia's formula

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Abbreviation	Term
qual	qualitative
R_{ac}	observed accumulation ratio for AUC_{τ}
$R_{ac,Cmax}$	observed accumulation ratio for C_{max}
RBA	relative bioavailability
RBC	red blood cell
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SARS-CoV-2 M^{pro}	the main protease of SARS-CoV-2
SCr	serum creatinine
Scys	serum cystatin C
SD	single dose; standard deviation
SDD	spray dried dispersion
SE	supratherapeutic exposure
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal half-life
TBD	to be determined
T bili	total bilirubin
TEAE	treatment-emergent adverse events
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UV-Vis	ultraviolet-visible spectroscopy
V_{ss}	steady-state volume of distribution
V_z/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

10.11. Appendix 11: Protocol Amendment History

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

Document	Version Date	Summary of Changes and Rationale
Amendment 2	**11 January 2023**	**Section 1.1 Synopsis:** The synopsis was aligned with the remainder of the protocol: PART-6 was added to objectives and endpoints; Overall Design was amended to reflect changes in PART-5 and the addition of PART-6; Number of Participants was updated to reflect the changes to PART-5 and addition of PART-6; Exclusion Criteria were updated with key criteria specific to PART-6; Study Interventions Table was updated to add Moxifloxacin for PART-6; PART-6 was included in Statistical Methods.
		Section 1.2.5: An optional Cohort 12 was added to the schema for PART-5 to potentially evaluate the effect of steady-state PF-07817883 at lower dose on the PK of midazolam in healthy adult participants.
		Section 1.2.6: Schema for PART-6 was added to evaluate safety, tolerability and PK of PF-07817883 at SE.
		Section 1.3.5: Changes were made to add the administration of PF-07817883 along with 5 mg midazolam on Day 5 in Treatment C for optional Cohort 12: Sequence 1: Midazolam dose in Period 2 Day 5 was added for optional Cohort 12 only; Sequence 2: Midazolam dose in Period 1 Day 5 was added for optional Cohort 12 only.
		Section 1.3.6: SoA (Table 9) for PART-6 was added to provide the Schedule of Activities for Part-6.
		Section 2.1: PART-6 was add to provide the study rationale.
		Section 2.2.2; Section 2.2.2.1; Section 2.2.2.2: Clinical safety data for PF-07817883 was added to provide clinical safety updates based on the preliminary data collected in PARTs 1 and 2 of this study.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Document	Version Date	Summary of Changes and Rationale
		Section 2.3.1: Risk assessment for moxifloxacin was added to provide potential risks related to the administration of moxifloxacin and the corresponding mitigation strategies.
		Section 3: Section 3.6 was added to include objectives and endpoints for PART-6: SE.
		Sections 4; 4.1.3; 4.1.5; 4.1.6: Text revised to reflect study design changes (removal of "optional") in PARTS 3, 4, and 5. Added 4.1.6 to include PART-6.
		Section 4.2.5: Scientific rationale for the optional Cohort 12 was provided.
		Section 4.2.6: Scientific rationale for PART-6 was added.
		Section 4.3: Added sections 4.3.2 to update the dose justification for PART-3, and 4.3.3 to include the dose justification for PF-07817883 and moxifloxacin in PART-6.
		Section 5.2: Exclusion criteria for PART-6 were added in the subsections "Prior/Concomitant Therapy" and "Other Exclusion Criteria" to exclude participants at increased risk if dosed with moxifloxacin, and participants with history or risk factors for QT prolongation or torsades de pointes, congenital deafness, family history of sudden death, and family history of long QT syndrome.
		Section 5.3.2: Restriction was added for PART-6 regarding the intake of ambient temperature or warm drinks from Day 1 until final ECG measurements have been collected in each study period for clarification purpose.
		Section 5.3.4: Activity for PART-1 only was updated to be for both PART-1 and PART-6 to standardize ECG collection and continuous cardiac monitoring..
		Section 6: Information related to moxifloxacin was added to provide information for moxifloxacin to be administrated in PART-6.
		Section 6.1.1.6: Administration details for PF-07817883/placebo and moxifloxacin were added to provide information for PF-07817883/placebo and moxifloxacin to be administrated in PART-6.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Document	Version Date	Summary of Changes and Rationale
		Section 6.2.1: Information related to moxifloxacin was added to provide information for moxifloxacin to be administrated in PART-6.
		Section 8.3.3: Requirements for ECG collection and continuous cardiac monitoring in PART-6 were added to standardize ECG collection and continuous cardiac monitoring.
		Section 8.5: A subsection (Section 8.5.3) was added for PK analysis of moxifloxacin to standardize the PK analysis of moxifloxacin in PART-6.
		Section 9.2: Description for ECG analysis set was added for purpose of analysis.
		Section 9.3.3.1.1: PF-07817883 and moxifloxacin PK parameters in PART-6 were added for purpose of analysis.
		Section 9.5: The number of cohort and/or participant in PARTs 1-5 was updated, and the justification for sample size in PART-6 was added to align with the current study design.
		Sections 1.2.1-1.2.5: Corresponding cohort number(s) was added to PARTs 1-5 for clarification.
		Section 9.3.5: The whole section was updated with addition of PART-6.
		Various sections: Spelling corrections and other editorial changes were made.
Amendment 1	**21 October 2022**	**Sections 1.3.1-2, and Section 8.3.1:** Post-dose physical exam (neuromuscular) was included to augment safety monitoring in line with FDA requests.
		Section 6.6.1: Dose escalation termination criterion based on neuromuscular exam was added and the dose escalation termination criterion for ECG was modified to augment safety monitoring in line with FDA requests.
		Sections 4.2 & 10.2: CK, PT, aPTT, INR, amylase and lipase were added to safety lab assessments to augment safety monitoring in line with FDA requests.
		Section 2.3.1: ECG was deleted.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Document	Version Date	Summary of Changes and Rationale
		Brief Title of Section 1.1: "Mass Balance" was updated to "Metabolism and Excretion" to align with Brief Title in the Title Page.
		Section 1.3 SOA: In Tables 1, 2, 4, 5, 6, and 7, SARS-CoV-2 RT-PCR only to be done at admission to align with the current practice.
		Sections 1.3.1-2: In Tables 1, 2, and 3, note for the row 12-Lead ECG (triplicate) was updated for clarification. In Tables 1 and 2, the first note was updated for clarification.
		Section 8.1: Total blood sampling volume was updated to allow additional safety labs.
		Section 1.3.3: In Table 4, note for "Contraception check", "Pregnancy test", "SARS-CoV-2 RT-PCR" and "COVID-19 signs and symptoms" rows were modified for clarity.
		Section 1.3.4: In Table 5, Day -1 was removed from the Drug related material measurement and metabolic profiling row as no need for testing at Day-1.
		Section 5.2: In the subsection of medical conditions, the 2 bullets that start with "PART-5 only" were updated to Exclusion Criteria #4 and #5.
		Section 5.3.2: In the subsection of Evening dosing condition, the text of "afternoon and/or" was removed as there is no afternoon dose
		Section 6.1.1.3: The second sentence "At a time point when PF07817883" was removed.
		Section 10.4.4: The paragraph below #5 Sexual Abstinence was updated to be a subsection of #5 instead of being #6. The below 2 sentences were underlined to keep consistent across the whole section: <u>Highly Effective Methods That Have Low User Dependency (for WOCBP partners of male participants)</u>

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

Document	Version Date	Summary of Changes and Rationale
		Highly Effective Methods That Are User Dependent (for WOCBP partners of male participants)
		Section 10.4.4: Added missing text describing effective barrier methods that must be used.
		Title Page and Section 1.1: ClinicalTrials.gov ID was added.
		Section 5.3.2: Post-dose food restriction in fed state was changed to 4h to make it consistent with EU guidance.
		Section 9.3.3.1.1: The PK parameters derivation for midazolam in PART-5 was defined in Table 14 to make it consistent with the title.
		Section 8: Blood volume was changed to allow additional clinical lab tests.
		Section 10.2: CKD-EPI formula was clarified.
		Section 3.5: Midazolam PK parameters calculations were clarified.
		Section 10.10: Added abbreviations appeared in added text.
		Various sections: Spelling corrections and other editorial changes were made.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

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.

2. Wu Z, McGoogan JM. 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 JS, 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 AB, Harrison EM, Green CA, 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. Centers for Medicare & Medicaid Services. COVID-19 Monoclonal Antibodies. Available from: https://www.cms.gov/monoclonal . Updated 10 Aug 2022. Accessed: 06 Sep 2022.

9. National Institutes of Health. COVID-19 Treatment Guidelines. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at https://www.covid19treatmentguidelines.nih.gov/. Updated: 18 Aug 2022. Accessed: 11 Aug 2022.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)

10. Singh RSP, Walker GS, Kadar EP, et al. Metabolism and excretion of nirmatrelvir in humans using quantitative fluorine nuclear magnetic resonance spectroscopy: a novel approach for accelerating drug development. Clin Pharmacol Ther. 2022;10.1002/cpt.2683.

11. Ramsden D, Zhou J, Tweedie DJ. Determination of a Degradation Constant for CYP3A4 by Direct Suppression of mRNA in a Novel Human Hepatocyte Model, HepatoPac. Drug Metab Dispos. 2015;43(9):1307-15.

[12] Huang DP, Chen J, Tsong Y. Baseline selection in concentration-QTc modeling: impact on assay sensitivity. J Biopharm Stat 2021;31(2):168-179. DOI: 10.1080/10543406.2020.1814797

[13] Garnett C, Needleman K, Liu J, Brundage R, Wang Y. Operational Characteristics of Linear Concentration-QT Models for Assessing QTc Interval in the Thorough QT and Phase I Clinical Studies. Clin Pharmacol Ther 2016;100(2):170-8. DOI: 10.1002/cpt.361.

[14] 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.

090177e19cda0704\Approved\Approved On: 09-Mar-2023 18:53 (GMT)