A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, 4-PERIOD, CROSSOVER, FIRST-IN-HUMAN STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SINGLE ASCENDING ORAL DOSES OF PF-07328948 ADMINISTERED TO HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07328948
Study Intervention Name:	NA
US IND Number:	CCI
EudraCT Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4921001
Phase:	1

Brief Title: A Phase 1 Study of Single Ascending Doses of PF-07328948 in Healthy Adult Participants

Document History

Document	Version Date
Amendment 2	24 Jan 2023
Amendment 1	29 Sep 2022
Original protocol	02 Sep 2022

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

Protocol Amendment Summary of Changes Table

Amendment 2 (24 Jan 2023)

Overall Rationale for the Amendment: The protocol is being amended to add pre- and post-dose neurological examinations to the Schedule of Activities and to extend CRU confinement of participants for an additional 24 hours to facilitate PK assessment at 72 hours post-dose. These changes are prompted by emerging safety and PK data from Cohort 1.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Sections 1.1 (Synopsis), 1.3 (Schedule of Activities), 2.3.1 (Risk Assessment), 2.3.2 (Benefit Assessment), 4.2 (Scientific Rationale for Study Design), 8.3.2 (Neurological Examinations), 9.3.1 (Safety Endpoints)	Updated to include neurological examinations pre- and post-dose, with relevant rationale.	A SAE of "possible seizure" occurred during follow-up in 1 participant in Cohort 1. Although not considered related to blinded study intervention by Pfizer safety assessment or Risk Management Committee, out of an abundance of caution, participants in this study will be monitored closely with serial physical exams directed at identifying any neurological signs or symptoms.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 4.1 (Overall Design), Section 4.2 (Scientific Rationale for Study Design), Section 4.3.1 (Human PK Predictions)	The participants in each treatment period will be confined in CRU for an additional day and discharged on Day 4 of Cohort 2 and optional Cohort 3 (changed from discharge on Day 3 in Cohort 1) to collect PK samples at 72 hours post-dose. The preliminary PK data emerging from Cohort 1 suggested the terminal half-life could be longer than this predicted 4 hours.	The emerging PK data from Cohort 1 suggested the terminal $t_{1/2}$ for PF-07328948 is longer than the previously predicted 4 hours based on preclinical data. Participants will stay in CRU for an additional day for PK assessment at 72 hours post-dose.	Substantial
Section 1.3 (Schedule of Activities), Section 5.3.2 (Meals and Dietary Restrictions)	CRU discharge, contraception check, physical exam, urinalysis, and safety laboratory tests removed from Day 3, and replaced as pre-discharge activities on Day 4; added “Day 4 (if applicable)” for meals and dietary resctrictions	As a result for one additional day confinement in CRU and discharge changed to Day 4, some assessments scheduled on Day 3 are moved to prior to discharge on Day 4.	Nonsubstantial
Section 1.3 (Schedule of Activities)	PK sample collection at 16 hours post-dose was removed.	PK sample at 16 hours was replaced by PK sample at 72 hours post-dose so the total blood volume withdrawn in each participant remains same	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, 4-Period, Crossover, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Ascending Oral Doses of PF-07328948 Administered to Healthy Adult Participants

Brief Title: A Phase 1 Study of Single Ascending Doses of PF-07328948 in Healthy Adult Participants

Regulatory Agency Identification Number(s):

US IND Number:	CCI
EudraCT Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4921001
Phase:	1

Rationale: This study is the first clinical study with PF-07328948. The safety, tolerability, and plasma PK and PD of PF-07328948 after administration of escalating, single, oral doses will be evaluated.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of single ascending doses of PF-07328948 administered orally to healthy adult participants.	• Assessment of adverse events, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead electrocardiograms, and physical examinations.
Secondary:	**Secondary:**
• To evaluate the pharmacokinetics of PF-07328948 following single doses of PF-07328948 administered orally to healthy adult participants.	• PK parameters derived from plasma PF-07328948 concentrations: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}, and $t_{½}$.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To evaluate additional pharmacokinetic parameters of PF-07328948 following single doses of PF-07328948 administered orally to healthy adult participants.	• Additional PK parameters derived from plasma PF-07328948 concentrations: C_{max}(dn), AUC_{last}(dn) and if data permit AUC_{inf}(dn), CL/F and V_z/F.
• CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
• To evaluate the effect of food (eg, a protein-rich meal such as MMTT), if administered, on the plasma PK of PF-07328948 following single dose of PF-07328948 administered orally to healthy adult participants.	• PK parameters derived from plasma PF-07328948 concentrations after MMTT: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}, and $t_{½}$.

Overall Design:

This is a randomized, investigator- and participant-blind, sponsor-open, placebo-controlled, first-in-human study to assess safety, tolerability, PK and PD of single ascending oral doses of PF-07328948 administered to healthy adult participants in 2 planned cohorts (Cohort 1 and Cohort 2). Each cohort will be a 4-period, sequential, crossover, placebo-controlled design, with a washout interval of at least 7 days between doses. Precautionary sentinel dosing will be used in any period evaluating escalating doses of PF-07328948. Sentinel dosing may be omitted for periods when repeating a dose level or administering a lower dose level than previously evaluated. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants

of that period. Participants will be screened for the eligibility criteria as listed in Section 5, within 28 days prior to administration of the first dose for each cohort.

Based on the review of emerging safety, tolerability, and PK, 1 optional cohort of 8 participants may be enrolled (crossover, placebo-controlled design) to explore additional doses, to repeat a dose, to evaluate split dosing, or to investigate food effects on PK and PD biomarkers.

CCI [redacted]

Number of Participants: A total of up to approximately 16 (Cohorts 1 and 2) or 24 (with optional Cohort 3) healthy adult participants (approximately 8 participants per cohort) will be enrolled in the study.

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

Study Population: Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

1. Female participants of non-childbearing potential and males must be 18 to 60 years of age, inclusive, at the time of signing the ICD.

2. Female participants of non-childbearing potential and males who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

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

Exclusion Criteria

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

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or

allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

- Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).
- History of 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. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention.

4. Receipt of a COVID-19 vaccine within 7 days before screening or within 7 days before any visit in which a safety lab is planned. Vaccination with a COVID-19 vaccine that occurs greater than 7 days from either screening or any visit in which a safety lab is planned is permitted.

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

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

7. Renal impairment as defined by an eGFR <75 mL/min/1.73m^2 calculated using CKD-EPI SCr formulas.

8. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate age myocardial infarction, STT 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.

9. 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 ≥1.25× 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.

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

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

Study Arms and Duration:

PF-07328948 and placebo will be provided by Pfizer as bulk powders for extemporaneous preparation of oral suspensions at the CRU.

Study Intervention(s)		
Intervention Name	PF-07328948	Placebo
Arm Name (group of participants receiving a specific treatment or no treatment)	PF-07328948	Placebo
Unit Dose Strength(s)	10-3000 mg	0 mg
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP

Study Arm(s)			
Arm Title	Cohort 1	Cohort 2	Cohort 3 (Optional)
Arm Type	Experimental	Experimental	Experimental
Arm Description	Participants will receive up to 4 dose levels of PF-07328948 and up to 2 doses of matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined.	Participants will receive up to 4 dose levels of PF-07328948 and up to 2 doses of matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined.	Participants will receive up to 4 dose levels of PF-07328948 and up to 2 doses of matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined.

Statistical Methods:

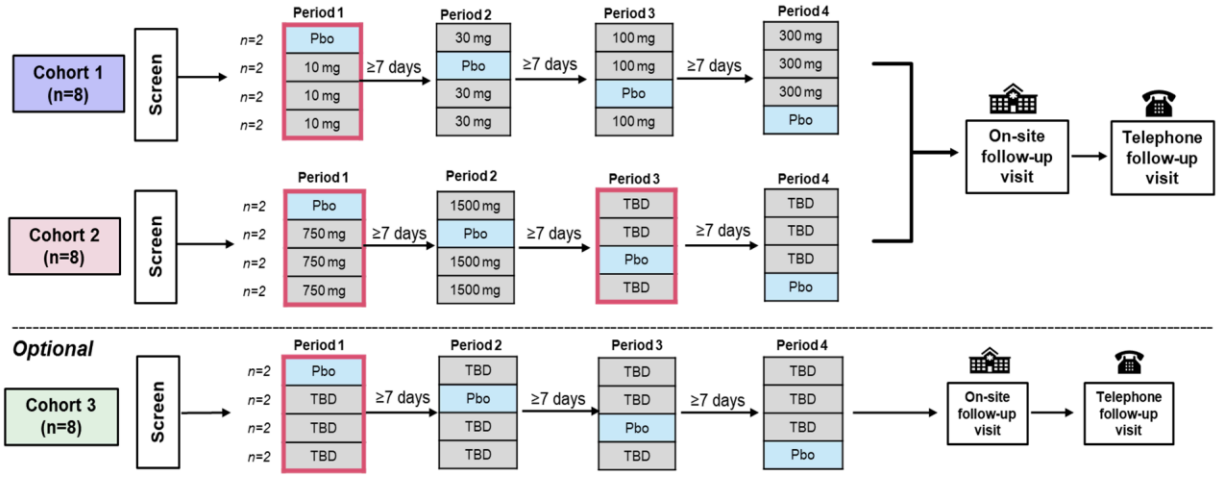
The sample size has been chosen based on the need to minimize first exposure to humans of a new chemical entity and the requirement to conduct adequate safety, toleration, PK and PD assessments at each dose level. All safety analyses will be performed on the safety analysis set, which is defined as all participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. The plasma PK parameters for PF-07328948 following oral dose administration will be derived from the plasma concentration-time profiles. Plasma PK parameters and concentrations of PF-07328948 will be descriptively summarized by dose (and fasting condition, if appropriate) and nominal time, as appropriate.

Ethical Considerations:

The participants in this study are not expected to obtain any specific benefit beyond contributing to the process of developing new therapies in an area of unmet need. They will receive close monitoring of their safety via study procedures undertaken (eg, physical examinations, neurological examinations, 12-lead ECGs, vital signs) which will occur as outlined in this protocol. Based on the totality of available nonclinical data, and taking into account the measures to minimize risk to study participants, the overall benefit/risk profile supports clinical testing of PF-07328948 in this study as part of the clinical development for an indication of heart failure.

1.2. Schema

Figure 1. Study Design Schema[a,b,c,d]



a. Doses shown for each cohort except the starting dose in Cohort 1 are planned doses and may be modified based on emerging data from previous cohorts. Similarly, assignment to study intervention may be modified. n represents number of participants

b. Effect of food (eg, a protein-rich meal such as MMTT) may be evaluated in at least 1 period of Cohort 2 (eg, P3) and/or Cohort 3

c. In the first period in each cohort (with red box) and the first period of assessment of food effect in any cohort (eg, P3 in Cohort 2 with red box), participants will be admitted on Day -2 and time-matched biomarker assessment will be collected on Day -1.

d. Precautionary sentinel dosing will be used in any period evaluating escalating doses of PF-07328948. For such periods, 2 participants (1 receiving PF-07328948 and 1 receiving placebo) will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period. Sentinel dosing may be omitted when repeating a dose level or administering a lower dose level than previously evaluated.

1.3. Schedule of Activities

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

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

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screen**	**Period 1 to Period 4 In-patient**							**Follow-Up**		**ET**	**Notes**
Days Relative to Day 1	**Day -28 to Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**		**Day 3**	**Day 4**	**Visit: Day 8±1**	**Contact: 28-35 days**		All screening should be done ≤28 days before the first dose. Day relative to start of study intervention (Day 1). Day 1 activities at time=0 hour are prior to the dose, except for study intervention administration. On-site follow-up visit occurs on Day 8±1 after administration of the final dose of study intervention. Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Hours After Dose				**0**	**24**	**36**	**48**	**72**				
Informed consent	X											Informed consent should be obtained prior to undergoing any study-specific procedures. See Section 10.1.3 for additional information.
CRU confinement		X	X	→	→	→	→	X				Admission on Day -2 only in Period 1 for each cohort and in the 1st period with assessment of food effect in any cohort, if applicable
Inclusion/exclusion criteria	X	X										Period 1 only. Review any changes from Screening.
Medical/medication history	X	X										
History of alcohol, tobacco, and illegal drug use	X	X										
Review concomitant treatments	X	→	→	→	→	→	→	→	→	X	X	See Section 6.9 for additional information.
Demography	X											

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screen**	**Period 1 to Period 4 In-patient**							**Follow-Up**		**ET**	**Notes**
Days Relative to Day 1	**Day -28 to Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**		**Day 3**	**Day 4**	**Visit: Day 8±1**	**Contact: 28-35 days**		All screening should be done ≤28 days before the first dose. Day relative to start of study intervention (Day 1). Day 1 activities at time=0 hour are prior to the dose, except for study intervention administration. On-site follow-up visit occurs on Day 8±1 after administration of the final dose of study intervention. Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Hours After Dose				**0**	**24**	**36**	**48**	**72**				
Contraception check	X	X	X					X	X	X	X	Contraception only required for male study participants. Contraceptive guidance is outlined in Appendix 4. If performed on Day -2 at admission, assessment is not needed on Day -1
COVID-19 related measures		X	X	X	X		X	X	X		X	Per CRU procedures.
CRU discharge								X				Participants may be asked to remain at the CRU after completion of Day 4 activities at the discretion of the investigator or if safety, tolerability, or PK data dictate the need to prolong inpatient stay at the CRU
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	X	X	See Section 8.4.3 for follow-up AE and SAE assessments.
Physical exam	X	X		See Table 2	X			X	X		X	Complete PE at Screening or upon admission for a participant's first period in the study; at all other time points, brief PE performed for findings during previous exam or new/open AEs, at investigator discretion. Including height and weight only at screening See Section 8.3.1 for additional information.
Neurological examination					X				X		X	Complete neurological exam for timepoints on Day 1 (see Table 2) and 24 hours after dosing on Day 1. At other time points, neurological exam at investigator discretion. See Section 8.3.2 for additional information.
Respiratory rate					X		X	X	X		X	Single assessment at all timepoints See Section 8.3.3 for additional details.

Table 1. Study Schedule of Assessment

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Days Relative to Day 1	**Day -28 to Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**		**Day 3**	**Day 4**	**Visit: Day 8±1**	**Contact: 28-35 days**		All screening should be done ≤28 days before the first dose. Day relative to start of study intervention (Day 1). Day 1 activities at time=0 hour are prior to the dose, except for study intervention administration. On-site follow-up visit occurs on Day 8±1 after administration of the final dose of study intervention. Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Hours After Dose				**0**	**24**	**36**	**48**	**72**				
Supine blood pressure and pulse rate	X				X		X	X	X		X	Single assessment at Screening, Day 1 at 0 hour, follow-up visit and ET. Triplicate assessments at all other times. Triplicate measures are collected approximately 2-4 minutes apart. See Section 8.3.3 for additional details.
12-Lead ECG	X				X		X	X	X		X	Single 12-lead ECG at Screening, follow-up visit and ET. Triplicate 12-lead ECGs at all other times. See Section 8.3.4 for additional details.
Continuous cardiac telemetry												
Study intervention administration												Dosing under fasted or fed conditions (eg, MMTT) is to occur as outlined in Section 5.3.2.
Standardized meal/snack		X	See Table 2		X		X					See Section 5.3.2 for detailed instruction.
Blood samples for:												
PF-07328948 plasma pharmacokinetics					X	X	X	X			X	See Section 8.5.1 for additional details.
CCI [redacted]			See Table 2	See Table 2	C		[redacted]		[redacted]		[redacted]	Samples on Day 2 and Day 3 (24 and 48-hours post-dose) and at follow-up visit (Day 8±1) after the final dose will be collected after fast overnight for at least 8 hours. See Section 8.7.2 for additional information.
CCI [redacted]							C				[redacted]	

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screen**	**Period 1 to Period 4 In-patient**							**Follow-Up**		**ET**	**Notes**
Days Relative to Day 1	**Day -28 to Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**		**Day 3**	**Day 4**	**Visit: Day 8±1**	**Contact: 28-35 days**		All screening should be done ≤28 days before the first dose. Day relative to start of study intervention (Day 1). Day 1 activities at time=0 hour are prior to the dose, except for study intervention administration. On-site follow-up visit occurs on Day 8±1 after administration of the final dose of study intervention. Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Hours After Dose				**0**	**24**	**36**	**48**	**72**				
Safety laboratory tests	X	X	X		X			X	X		X	Participant should fast for at least 4 hours prior to sample collection. If performed on Day-2 at admission, safety lab tests are not needed on Day -1. Results of any pre-dose safety labs should be reviewed and confirmed acceptable prior to dosing.
Retained Research Sample for Genetics (Prep D1.5)				X								Collected in first period only. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. See Section 8.6.2 for additional details.
Pfizer Prep B1.5 retained research sample				X	X							Samples to be collected as outlined in Section 8.7.1.4. Samples will be collected in Period 1 and Period 4 only for each cohort
Pfizer Prep B2.5 retained research sample				X	X							
HIV, HBsAg, HBsAb, HBcAb, HCVAb	X											See Appendix 2: Clinical Laboratory Tests.
FSH	X											Only for females who have been amenorrheic for at least 12 months.
Urine samples for:												
Urine drug testing	X	X	X									If performed on Day-2 at admission, urine drug testing is not needed on Day -1. Results of any pre-dose testing should be reviewed and confirmed acceptable prior to dosing. See Appendix 2: Clinical Laboratory Tests

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screen**	**Period 1 to Period 4 In-patient**							**Follow-Up**		**ET**	**Notes**
Days Relative to Day 1	**Day -28 to Day -3**	**Day -2**	**Day -1**	**Day 1**	**Day 2**		**Day 3**	**Day 4**	**Visit: Day 8±1**	**Contact: 28-35 days**		All screening should be done ≤28 days before the first dose. Day relative to start of study intervention (Day 1). Day 1 activities at time=0 hour are prior to the dose, except for study intervention administration. On-site follow-up visit occurs on Day 8±1 after administration of the final dose of study intervention. Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Hours After Dose				**0**	**24**	**36**	**48**	**72**				
Urinalysis (with microscopy, if needed)	X	X	X		X			X	X		X	Participant should fast for at least 4 hours prior to sample collection. If performed on Day-2 at admission, urinalysis not needed on Day -1. Results of any pre-dose testing should be reviewed and confirmed acceptable prior to dosing. See Appendix 2: Clinical Laboratory Tests

Table 2. Schedule of Activities for PK, PD, Vitals, and ECGs on Day 1 (and Day -1 if Applicable)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.													**Notes**
	Day 1, Day -1 (if applicable)												**Applies to Day 1 for Periods 1-4, and for Day -1 when admission occurs on Day -2**
Hours Relative to Dosing at 0 hour	**-1.0**	**-0.5**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**10**	**12**	Day 1 activities at time = 0 hour are prior to the dose, except for study intervention administration.
Study intervention administration (Day 1 only)			X										Dosing under fasted or fed conditions (eg, MMTT) is to occur as outlined in Section 5.3.2.
Standardized meal/snack									X		X		See Section 5.3.2 for detailed instruction. Participants will be provided the same lunch, dinner and snacks at same times on Day -1 when time-matched biomarker assessment is collected and on Day 1 of each period. If administered on Day -1, MMTT will be administered at the same time as planned for administration on Day 1 (ie, 20 minutes prior to 0 hour).
High protein meal (eg, MMTT)			X										Administered only in periods where food effect is assessed. See Section 5.3.2 for detailed instruction. High protein meal to be provided approximately 20 minutes prior to 0 hours, and consumed within 10 minutes such that study intervention is administer approximately 10 minutes after completion of meal.
Continuous cardiac telemetry (Day 1 only)			X	→	→	→	→	→	→	X			To establish a baseline, telemetry should be recorded for at least a 2-hour interval before dosing in Period 1, either immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing when the participant is awake. See Section 8.3.4.1. Assessment on Day 1 initiate at time=0 and continue through 8 hours post dose.
Neurological examination			X				X						Day 1 only. The pre-dose assessment (at time =0 hr) can be completed at any time within 24 hours prior to the dose on Day 1 in each period.
12-Lead ECG (Day 1 only)	X	X	X		X		X	X	X	X		X	Triplicate measures are collected approximately 2-4 minutes apart. See Section 8.3.4 for additional details.
Supine BP and pulse rate (Day 1 only)			X		X		X	X	X	X		X	Single measurement only at 0 hour; triplicate measurement at other timepoints. Triplicate measures are collected approximately 2-4 minutes apart. See Section 8.3.3 for additional details.
Respiratory rate (Day 1 only)			X		X		X	X	X	X		X	Single assessment at all timepoints See Section 8.3.3 for additional details.

Table 2. Schedule of Activities for PK, PD, Vitals, and ECGs on Day 1 (and Day -1 if Applicable)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.												**Notes**
	Day 1, Day -1 (if applicable)											**Applies to Day 1 for Periods 1-4, and for Day -1 when admission occurs on Day -2**
Hours Relative to Dosing at 0 hour	**-1.0**	**-0.5**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**10**	**12**	Day 1 activities at time = 0 hour are prior to the dose, except for study intervention administration.
PF-07328948 plasma pharmacokinetics (Day 1 only)			X	X	X	X	X	X	X	X		X	See Section 8.5.1 for additional information.
CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]
CCI [redacted]		[redacted]	[redacted]				[redacted]		[redacted]		[redacted]		

2. INTRODUCTION

PF-07328948 is a small molecule allosteric inhibitor/degrader of BDK that is currently being developed as an oral therapy to treat heart failure.

2.1. Study Rationale

This study will be the first time PF-07328948 is administered to humans. The purpose of the study is to evaluate the safety, tolerability, plasma PK and PD of PF-07328948 following administration of escalating, single, oral doses to healthy adult participants.

2.2. Background

Tissue and/or plasma BCAA and/or BCKA levels are elevated in various disease states including heart failure, type 2 diabetes mellitus, NAFLD/NASH, and obesity.[1,2,3,4] Furthermore, elevated BCAA levels in HF are associated with a loss of the BCAA catabolic machinery,[1,2] suggesting that the BCKDH pathway, involved in BCAA and BCKA catabolism, is dysregulated in cardiometabolic disease indications. Because inhibitory phosphorylation of BCKDH by BDK reduces BCAA catabolism, a BDK inhibitor would reduce BCKDH phosphorylation, thereby increasing BCAA and BCKA catabolism and reducing the elevated levels of BCAAs and BCKAs associated with several cardiovascular and metabolic diseases.

PF-07328948 is an orally administered, small molecule, potent allosteric BDK inhibitor that inhibits BCKDH phosphorylation in vitro and has consistently demonstrated robust, dose- and time-dependent BCAA and BCKA lowering in plasma and tissues in mouse, rat and/or CCI [redacted] These improvements were concomitant with reduced pBCKDH and BDK levels in heart and kidney tissue as well as reduced plasma BCAA and BCKA levels.

2.2.1. Nonclinical Pharmacology

PF-07328948 is a potent antagonist of mouse, rat, dog, and human BDK CCI [redacted] In human skeletal muscle cells, PF-07328948 treatment resulted in inhibition of BDK-dependent phosphorylation of BCKDHA. In HEK293 cells, PF-07328948 decreased both BDK protein and the ratio of pBCKDHA/BCKDHA protein. CCI [redacted]. In diet-induced obese mice, reductions of plasma BCAAs and BCKAs were observed following subchronic and chronic dosing. PF-07328948 reduced liver triglycerides, plasma insulin levels, and plasma non-esterified free fatty acids after chronic dosing compared with vehicle-

treated animals. These metabolic improvements were concomitant with decreases in BDK protein levels in gastrocnemius muscle and heart, and decreased phosphorylation of BCKDH in muscle, heart, and liver. In the ZSF1 rat model of heart failure-preserved ejection, after chronic administration in food, PF-07328948 improved exercise capacity and increased systolic cardiac functional parameters, with a trend for reduced left atria hypertrophy compared to animals that were administered control chow. These improvements were concomitant with reduced pBCKDH and BDK levels in heart and kidney tissue as well as reduced plasma BCAA and BCKA levels.

Details of the nonclinical pharmacology are included in the IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

PF-07328948 was rapidly absorbed with moderate to high oral bioavailability and had low to moderate plasma CL and V_{ss} in rats, dogs, and monkeys. After IV administration of PF-07328948, renal excretion of unchanged PF-07328948 was <1% in rats, dogs, and monkeys and biliary excretion of unchanged PF-07328948 was ~1% in rats. In oral repeat-dose toxicity studies in rats and dogs, the systemic exposure increased with increasing dose in a less than or approximately dose proportional manner and there were no consistent sex-related differences or accumulation observed.

PF-07328948 was highly bound to plasma proteins in all species evaluated, with binding that was concentration dependent and was preferentially distributed into plasma relative to blood CCI

The DDI potential was further evaluated with a static mechanistic model using the projected C_{max} for reversible inhibition or C_{ave} for induction in plasma, intestinal lumen, enterocytes, liver, and portal inlet. CCI

CCI [redacted] These predictions will be refined once human PK data are available for PF-07328948.

Additional details are included in the IB.

CCI [redacted]

2.2.4. Nonclinical Safety

PF-07328948 was administered orally to rats and dogs in toxicity studies up to 1 month in duration. CCI [redacted] The NOAEL in the 1-month GLP repeat-dose toxicity study in rats was 100 mg/kg/day, CCI [redacted]. The NOAEL in the 1-month GLP repeat-dose toxicity study in dogs was 100 mg/kg/day, CCI [redacted]

Based on a weight of evidence, PF-07328948 does not pose a risk for genotoxicity.

Based on the UV absorption profile of PF-07328948, there is a potential for phototoxicity.

Additional details of the nonclinical safety are provided in the IB.

2.3. Benefit/Risk Assessment

Study C4921001 is the first time that PF-07328948 will be administered to humans and is designed primarily to generate safety, tolerability, and PK and PD data for further clinical development. PF-07328948 is not expected to provide any clinical benefit to healthy participants. The purpose of this study is to provide the basis for further clinical development of PF-07328948 as a first-in-class therapy for treatment of patients with heart failure. As of the date of final protocol, no specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.3.1. The clinical impact of these potential risks will be minimized through the proposed cautious dose-escalation process wherein higher doses of PF-07328948 will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile. Use of stopping rules for dose-escalation, as well as by specific safety monitoring measures, have been incorporated into this study, where appropriate, as outlined in the SoA. In addition, this study will use precautionary sentinel dosing in periods evaluating escalating doses of PF-07328948, and all periods will include 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-07328948 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

All study intervention risks are communicated through the IB.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention - PF-07328948		
Effects on blood pressure	Decreased BP was observed after single doses (≥ 20 mg/kg) of PF-07328948 in dogs in exploratory toxicology studies. No BP changes were subsequently noted in GLP toxicology studies after single doses of ≤ 100 mg/kg in dogs.	• Participants will be in a closely monitored environment while in the CRU during the study. • Inpatient monitoring will include serial assessment of blood pressure.
Skin sensitivity to light; sunburn	Based on light absorption within the UV range, PF-07328948 has a risk for phototoxicity.	• Participants with a history of phototoxicity or photosensitivity are excluded from study. • Lifestyle and activity considerations have been added advising participant to use sunscreen and eye protection, and to avoid sunlight and high-intensity UV light exposure.
Drug-drug interactions resulting in exposure changes of background concomitant medications.	CCI [redacted]	• Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention through the last PK collection.
Idiosyncratic drug reaction	IADR risk CCI [redacted]	• Participants will be in a closely monitored environment while in the CRU during the study. • Risk of IADR after single dose of PF-07328948 is considered low. • Laboratory safety tests include serial assessment of LFTs and CBCs.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
BCAA deficiency	BCAAs play a multifaceted role in maintenance of health. Prolonged deficiency of ≥ 1 BCAA caused by excessive dietary restrictions in children associated with neurodevelopmental delays-function mutations in BDK gene in humans are associated with neurological sequelae.	• Single doses of PF-07328948 are not anticipated to result in prolonged lowering of BCAAs. • Risk of neurological sequelae from magnitude and duration of BCAA lowering expected following single doses of PF-07328948 is considered very low. Neurological examination as part of the physical exam will be performed pre- and post-dose.
Other		
The COVID-19 pandemic may pose risks to study participation.	During the pandemic, healthy participants could be infected with the SARS-CoV-2 virus through study participation, which could lead to increased health risks for this participant and others in the study. AEs could be confounded.	• Inclusion of COVID-19 specific assessments according to the SoA.

2.3.2. Benefit Assessment

The participants in this study are not expected to obtain any specific benefit beyond contributing to the process of developing new therapies in an area of unmet need. They will receive close monitoring of their safety via study procedures undertaken (eg, physical examinations, including neurological examinations, 12-lead ECGs, vital signs) which will occur as outlined in this protocol.

2.3.3. Overall Benefit/Risk Conclusion

Based on the totality of available nonclinical data, and taking into account the measures to minimize risk to study participants, the overall benefit/risk profile supports clinical testing of PF-07328948 in this study as part of the clinical development for an indication of heart failure.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of single ascending doses of PF-07328948 administered orally to healthy adult participants.	• Assessment of adverse events, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead electrocardiograms, and physical examinations.
Secondary:	**Secondary:**
• To evaluate the pharmacokinetics of PF-07328948 following single doses of PF-07328948 administered orally to healthy adult participants.	• PK parameters derived from plasma PF-07328948 concentrations: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}, and $t_{½}$.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To evaluate additional pharmacokinetic parameters of PF-07328948 following single doses of PF-07328948 administered orally to healthy adult participants.	• Additional PK parameters derived from plasma PF-07328948 concentrations: C_{max}(dn), AUC_{last}(dn) and if data permit AUC_{inf}(dn), CL/F and V_z/F.
• CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
• To evaluate the effect of food (eg, a protein-rich meal such as MMTT), if administered, on the plasma PK of PF-07328948 following single dose of PF-07328948 administered orally to healthy adult participants.	• PK parameters derived from plasma PF-07328948 concentrations after MMTT: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}, and $t_{½}$.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, investigator- and participant-blind, sponsor-open, placebo-controlled, first-in-human, single ascending oral dose, 4-period, sequential, crossover study of PF-07328948 administered to healthy adult participants. Approximately 24 healthy adult participants (up to 3 cohorts of approximately 8 participants each) will be enrolled in this study. The first 2 cohorts are planned, and the third cohort is optional. In each period, participants will be randomized to either PF-07328948 or placebo in a ratio of 3:1. Each participant is planned to undergo up to 4 treatment periods receiving up to 4 doses of PF-07328948 and up to 2 placebo.

Precautionary sentinel dosing will be used in any period evaluating escalating doses of PF-07328948 and may be omitted for periods when repeating a dose level or administering a lower dose level than previously evaluated. For periods with sentinel dosing, 2 participants (1 receiving PF-07328948 and 1 receiving placebo) will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period.

Participants confirming eligibility according to Section 5 will be admitted to the CRU on Day -2 in Period 1 for each cohort and the 1st food period (if applicable) within a cohort. For all other periods (ie, Periods 2-4 except the 1st food period within each cohort), participants will be re-admitted to the CRU on Day -1. For each period in this study, on Day 1, following ≥10-hour overnight fast, participants will receive a single oral dose of PF-07328948 or placebo. Participants have been discharged on Day 3 in Cohort 1 and will be discharged on Day 4, following completion of all scheduled assessments out to 72 hours post-dose in Cohort 2 and optional Cohort 3. Participants may stay in the CRU after completion of Day 4 activities at the discretion of the investigator. In each cohort, a washout interval of at least 7 days will be introduced between subsequent doses. During the washout interval, emerging 24-hour PK and 48-hour safety data will be reviewed and the next dose will be determined. An on-site follow-up visit on Day 8±1 after the final dose and a final follow-up within 28-35 days after the final dose will be scheduled. Final follow-up may be a phone contact or an on-site visit at the discretion of the PI.

Based on the review of emerging safety, tolerability, and PK data (and PD data if available) in Cohorts 1 and 2, the optional third cohort may enroll 8 participants (crossover, placebo-controlled design) to explore additional doses, to repeat a dose, to evaluate split dosing, or to investigate food effects on PK and PD biomarkers.

Dosing will occur in the fasted state for all periods for dose escalation. The effect of a high-protein meal on safety, tolerability, PK exposure, and PD biomarkers CCI [redacted] may be assessed in at least 1 period within Cohort 2 and/or Cohort 3. CCI [redacted]

CCI [redacted] Participants should only need to undergo these time-matched assessments of PD biomarkers on Day -1 once in the fasted state and/or once in the fed state in each cohort, unless there is any uncertainty regarding the reliability of the initial Day -1 assessment. In addition, if thought necessary to achieve study objectives, study intervention may be administered in the fed state (eg, following a high-protein meal) during any of the study periods/cohorts.

The total duration of participation from the screening visit to the telephone follow-up contact will be approximately 14 weeks.

If a participant drops out before completing all study periods within a cohort, or withdraws for a reason unrelated to safety, the participant may be replaced at the discretion of the investigator 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 investigator and sponsor. Of note, replacement participants may be required to undergo time-matched assessments of PD biomarkers during Day -1 of their initial period in the study.

4.2. Scientific Rationale for Study Design

The population planned for this study will be healthy males and females of non-childbearing potential. Female participants will be confirmed not to be of childbearing potential because embryo-fetal development toxicity studies with PF-07328948 have not been conducted. In male participants, appropriate measures are expected to be followed to minimize potential transfer of PF-07328948 via semen to partners (see Appendix 4).

Because this is the first time PF-07328948 will be administered to humans, an escalating single, oral dose, crossover design is planned with careful assessment and ongoing review of safety, tolerability, and PK data of PF-07328948. Precautionary sentinel dosing will also be utilized in any period evaluating escalating doses of PF-07328948 to ensure that safety and tolerability data in a subset of 2 participants within each period supports testing additional participants in that period. In each period, approximately 6 participants are planned to receive PF-07328948, and approximately 2 participants are planned to receive placebo, with all the participants at the end of the study having received up to 4 doses of PF-07328948 and up to 2 placebo. The crossover design permits both within- and between-participants assessments of safety, tolerability, and PK at multiple dose levels and placebo.

In addition, the highest anticipated C_{max} and AUC_{24} of PF-07328948 will not exceed the pre-defined human exposure stopping limits nor exceed the highest feasible total daily dose CCI [redacted]. Furthermore, to permit an unbiased assessment of safety, the administration of both PF-07328948 and placebo in each period will be double-blinded to both site staff (except those involved in preparation of doses) as well as participants. To permit real-time review of the safety, tolerability, and PK data, a limited number of sponsor study team members will be unblinded.

CCI [redacted]. As a BDK inhibitor/degrader,

PF-07328948 is expected to inhibit BDK-mediated phosphorylation of BCKDH enzyme complex, resulting in an increase in BCAA/BCKA catabolism and a decrease in circulating BCAA and BCKA levels. As protein intake is known to impact plasma BCAA/BCKA levels,[5] CCI [redacted]. Lunch and dinner will be standardized when participants are confined in the CRU; additional efforts will be made to ensure lunch, dinner and snacks are as identical as is feasible on Day 1 for each period and on Day -1 where time-matched CCI [redacted] assessment is performed (Section 5.3.2). CCI [redacted]

CCI [redacted]

Based on predicted half-life in human (~4 hours), PK samples were collected over 48 hours post-dose in Cohort 1. However, the preliminary PK data emerging from Cohort 1 suggested the terminal half-life could be longer than the predicted 4 hours therefore, participants in remaining Cohort 2 and optional Cohort 3 will be confined in CRU up to Day 4 with PK samples collected up to 72 hours post-dose. A washout interval of ≥7 days is proposed between doses within an individual participant; this interval should be sufficient based on all emergent PK data to date, and the projections that CCI [redacted] levels return to baseline within approximately 72 hours post-dose based on a PK/PD model developed with preclinical data and emergent PK/PD data in Cohort 1. In addition, this washout interval should offer sufficient opportunity to review safety, tolerability, and PK data after each dosing period prior required for decision on the PF-07328948 dose to be evaluated in the subsequent period. However, sampling times, duration of sampling, and/or the length of the washout period may be modified and/or extended based on emerging PK and/or PD data. Participants may be asked to remain at the CRU after completion of Day 4 activities at the discretion of the investigator or if safety, tolerability, or PK data dictate the need to prolong inpatient stay in the CRU. The planned doses and assignment to study intervention in the escalation sequence (see Section 1.2) may be modified or repeated, as guided by emerging safety, tolerability, and PK data but will follow the dose-escalation rules defined in Section 6.6.1.

Decreased blood pressure was observed after single doses (≥ 20 mg/kg) of PF-07328948 in dogs in exploratory toxicology studies; however, no significant blood pressure changes were subsequently noted in GLP toxicology studies after single doses of ≤ 100 mg/kg in dogs. Serial triplicate assessment of blood pressure will be performed following single dose administration as outlined in SoA. Triplicate 12-lead ECGs and continuous cardiac telemetry

also will be monitored as outlined in SoA. PF-07328948 effects on the respiratory system included transiently lower tidal volume and minute volume in rats at 100 mg/kg in the GLP-compliant pulmonary assessment study. The relevance of these transient effects of PF-07328948 on rat tidal and minute volume to humans is unknown, but respiratory rate will be monitored in the clinic.

One serious adverse event was reported during the follow-up period in 1 participant (out of 9 participants) in the first cohort of this study. This participant completed 4 periods of the study, and received single doses of PF-07328948 in each of 3 periods and a single dose of placebo in 1 period per protocol, with at least 7 days between doses. An adverse event of "loss of consciousness, possible seizure" was reported in this participant during the follow-up period, 7 days following the last dose of blinded study medication (PF-07328948 or placebo) administered in Period 4. The participant required assessment in the Emergency Department for this adverse event, but spontaneously resolved without intervention and did not require hospitalization or any specific treatment. While the Principal Investigator could not exclude the possibility that the blinded study medication (PF-07328948 or placebo) may have contributed to the adverse event of "loss of consciousness, possible seizure", this event was also reviewed by the Pfizer safety team and by a Pfizer Risk Management Committee, and these teams concluded that the event was unrelated to study intervention based on the prolonged duration between last dose of blinded study medication and animal data indicating that PF-07328948 does not cross the blood-brain barrier. In addition, no seizures were observed in any of rat or dog studies described above. Out of an abundance of caution, however, participants in this study will be monitored closely with serial physical exams directed at identifying any neurological signs or symptoms.

Based on the UV absorption profile of PF-07328948, there is a potential for phototoxicity and so participants will be advised to take necessary precautions to avoid direct sunlight exposure or any high intensity UV light exposure from admission in Period 1 through the follow-up contact, as described in Section 5.3.4.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for PF-07328948. Therefore, the use of a highly effective method of contraception is required for male study participants and is recommended for partners of male study participants who are WOCBP (see Appendix 4).

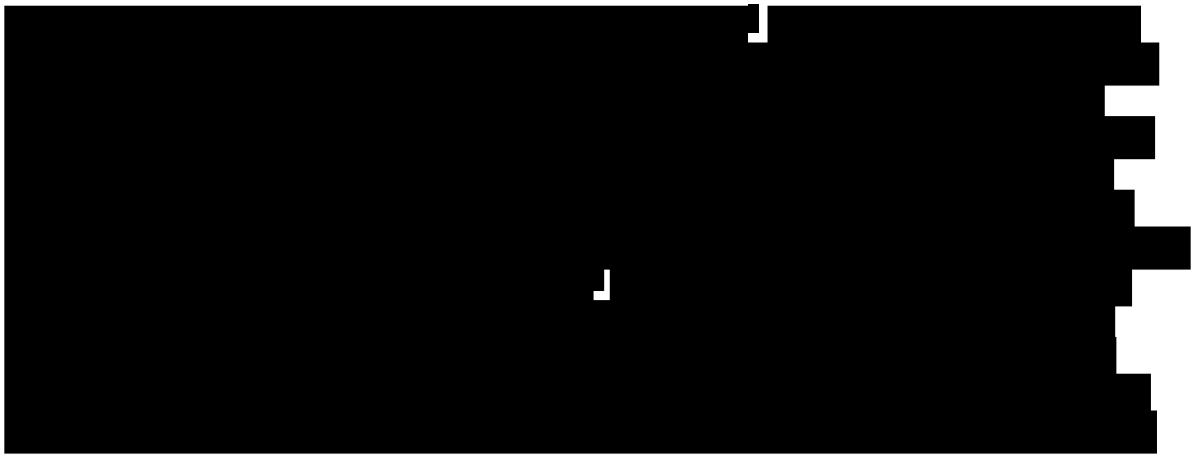
4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

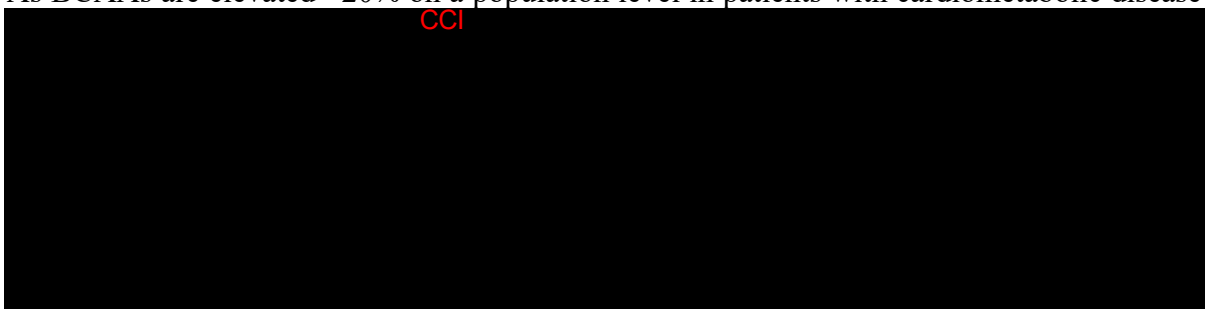
The proposed dose levels of PF-07328948 were derived based on cumulative nonclinical data, including in vitro, in vivo, PK and PD data, and the completed nonclinical toxicity studies. Dose levels beyond the starting dose (in Period 1 of Cohort 1) may be modified based on emerging human safety, tolerability, and PK data in the current study.

CCI [redacted]



4.3.2. Predicted Efficacious Concentration and Human Dose

The desired degree of target modulation is based on published human metabolomic data.[3,4,7,8] As BCAAs are elevated ~20% on a population level in patients with cardiometabolic disease CCI [redacted]



However, due to uncertainty around the degree of target modulation necessary for efficacy in patients with heart failure and the first-in-class nature of the mechanism of BDK inhibition, higher degrees of target modulation CCI [redacted] is desired to be evaluated if permitted by safety data.

4.3.3. Human Exposure Stopping Limits

The NOAELs in the pivotal 1-month GLP toxicity studies were CCI [redacted] which correspond to the highest doses tested in those respective studies.

Therefore, the human exposure stopping limits for PF-07328948 are based on unbound exposures at the NOAEL CCI [redacted] observed in the 1-month GLP toxicity study in rats which is defined as the most sensitive species.

- The human PF-07328948 C_{max} limit is CCI [redacted]
- The human PF-07328948 AUC_{24} limit is CCI [redacted]

4.3.4. Rationale for Dose Selection

The safety, tolerability, and plasma PK of PF-07328948 after administration of single escalating oral doses across a wide dose/exposure range will be evaluated in this study. Dosing will occur in the fasted state, except in periods in which dosing may occur in the fed state to permit exploratory assessment of the effect of food on PF-07328948 PK and PD. The doses presented in Table 3 are projected based on nonclinical data and may be modified based on emerging human safety, tolerability, and PK data. Predicted human PK parameter estimates, toxicokinetic data, and projected efficacious concentrations were used to establish the initial range of planned doses in this study. The projected human exposures account for concentration-dependent protein binding within the planned dose range.

Table 3. Predicted Human Exposures, Pharmacodynamic Effects, and Safety Margin at Proposed Single Doses of PF-07328948

Dose (mg)	C_{max}[a] (ng/mL)		AUC_{24}[a] (ng.h/mL)		CCI							
	Total	Free	Total	Free	CCI							
10	461	1	2990	4	C							
30	1380	2	8910	11	C							
100	4610	6	29000	37	C							
300	13800	20	81500	112	C							
750	34600	64	181000	286	C							
1500	69200	173	310000	595	C							

a. Human PK profiles were predicted using a 1-compartment model with the projected human PK parameters for PF-07328948 outlined in Section 4.3.1. Human plasma fu values were predicted using the linear equation (CCI and hepatic clearance was projected using the well-stirred model.
b. Pharmacodynamic effects elucidated with Ile and KMV was simulated based on a PK/PD model developed with preclinical data and Ki for human BDK inhibition and human fasting plasma Ile and KMV baseline level. Ave reduction was calculated over 24 hours.
c. SM, safety margin for unbound exposure (Cmax,u and AUC24,u) at the proposed doses were calculated based on the NOAELs in the 1-month GLP toxicity studies in both rats and dogs. The human exposure limits were defined as CCI observed at NOAEL in rat 1-month GLP toxicity study.

The PF-07328948 starting dose level of 10 mg is planned. The predicted PF-07328948 $C_{max,u}$ and $AUC_{24,u}$ after single dose of 10 mg are CCI, respectively, below the exposure limits defined for PF-07328948 dose escalation in Section 4.3.3. The maximum reduction for plasma isoleucine and ketoisoleucine are predicted to be 3% and 4%, respectively, suggesting little target modulation at this dose. A single dose of 1500 mg (the top dose in Table 3) is estimated to provide an exposure margin CCI , respectively, relative to the exposure limits.

The dose range to be studied was selected to account for uncertainties in the projected C_{eff} and the projected therapeutic dose, while also bracketing the expected clinically effective dose range in humans for clinically relevant pharmacological activity and providing safety coverage for a wide range of PF-07328948 doses.

Assessment of the safety, tolerability, and PK after each single dose level will be conducted before escalating to the next dose level. The dose/exposure-escalation increments are planned to be up to approximately semi-logarithmic increases in exposure from the previous highest dose level that has been evaluated. If exposure exceeds the projected therapeutic range, or if changes in safety parameters are observed, smaller dose-escalation steps may be implemented.

The actual dose levels, target exposures, and/or dose level increments may be adjusted (higher or lower) during the study based on emerging human safety, tolerability, and PK data, but projected exposures will not exceed the predefined human exposure limits. If C_{max}-related adverse events are observed, split dosing (eg, the total dose will be divided into 2 or 3 parts on Day 1) may be used to potentially increase AUC without increasing C_{max}. Dose levels may also be repeated if warranted.

When the assessment of the effect of food on the PK and PD of PF-07328948 is conducted, the dose level will be selected based on emerging safety, tolerability, and PK data from previous periods of this study. The actual dose level used will be expected to achieve exposures similar to or greater than projected therapeutic exposures (as outlined in Section 4.3.2).

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.

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 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, and 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. Female participants of non-child bearing potential and males must be 18 to 60 years of age, inclusive, at the time of signing the ICD.

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

2. Female participants of non-child bearing potential and males who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

Other Inclusion Criteria:

3. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

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

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

   - 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.

   - History of phototoxicity or photosensitivity.

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.

Prior/Concomitant Therapy:

3. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention through the last PK collection, with the exception of moderate/strong CYP3A inducers or time-dependent inhibitors which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

4. Receipt of a COVID-19 vaccine within 7 days before screening or within 7 days before any visit in which a safety lab is planned. Vaccination with a COVID-19 vaccine that occurs greater than 7 days from either screening or any visit in which a safety lab is planned is permitted.

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

6. A positive urine drug test.

7. 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.

8. Renal impairment as defined by an eGFR <75 mL/min/1.73m^2 (based on serum creatinine). Based upon participant age at screening, eGFR is calculated from serum creatinine using the recommended CKD-EPI SCr formulas in Section 10.7.2 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events.

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

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

    - AST **or** ALT level ≥1.25 × 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:

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

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

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

14. Use of tobacco or nicotine-containing products in excess of the equivalent of 5 cigarettes/day or 2 chews of tobacco/day.

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

16. 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.

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

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

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations, and at least 10 hours prior to the collection of the pre-dose PK and PD biomarker samples on Day 1 (and on Day -1 if relevant for that period), and at least 8 hours prior to PD biomarker collection on Day 2, Day 3, Day 4 (if applicable) and Day 8 ±1 visit (following final dose of study intervention).

- Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices-see below) may be consumed with meals and the evening snack.

- Dosing under fasted conditions:

    - Following an overnight fast of at least 10 hours, participants will receive study intervention.

    - Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing.

    - No food or drink (other than water) is permitted until lunch approximately 4 hours after dosing and ***after*** the 4-hour post-dose blood collection samples have been completed.

- Dosing when an effect of a protein-rich meal (eg, MMTT) is investigated, if performed:

    - Following an overnight fast of at least 10 hours, participants will be provided a protein-rich meal as 16 ounces of Ensure Plus® breakfast approximately 20 minutes prior to administration of study intervention. The entire Ensure Plus® meal is to be consumed within 10 minutes with study intervention administered approximately 10 minutes after completion of the meal at 0 hour. There are no water restrictions prior to dosing for participants dosed under fed conditions. Water may be consumed without restriction beginning 1 hour after dosing.

- MMTT on Day -1, if administered:

    - Following an overnight fast of at least 10 hours, participants will be provided a protein-rich meal as 16 ounces of Ensure Plus® breakfast; the timing of administration of the protein-rich meal on Day -1 will be at approximately the same time as planned for administration on Day 1.

- Lunch will be provided approximately 4 hours after dosing and ***after*** the 4-hour postdose samples (or time-match sample on Day -1 if applicable) have been collected.

- Dinner will be provided approximately 10 hours after dosing and ***after*** the 10-hour postdose samples (or time-matched sample on Day -1 if applicable) have been collected.

- An evening snack may be permitted. Participants will receive the same evening snack at approximately the same time (± 30 minutes) on Day -1 and Day 1, as well as on any Day -2 if applicable.

- Participants will be provided the same lunch, dinner and snacks on Day -1 when time-matched biomarker assessment is collected and on Day 1 of each period (with or without a MMTT) to strive for as similar food intake as is feasible on these days across periods.

- Participants will be encouraged to consume their entire meals on Day 1 during all periods. In addition, participants will be encouraged to consume their entire evening snack (if applicable) on Day -2 and entire meals on Day -1 if a MMTT is planned for Day -1; if participants do not consume their entire meal on Day -1 where a MMTT is performed, they will be instructed to consume the same amount of food (±10%, with similar uptake of optional snacks) on following Day 1 that they ate on Day -1. The approximate percentage of food consumed for these meals should be recorded in the CRF based on visual assessment by the site staff. Participants will not be required to consume all provided food during standard meals on other study days.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal. However, these guidelines may be adapted to facilitate meal and dietary restrictions required for Day 1 in each period and for Day -1 when time-matched biomarker assessment is collected with or without a MMTT.

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, pulse rate, and ECG measurements), eating, and drinking beverages, other than water, during the first 4 hours after dosing.

- Participants will be confined to the procedure room for the first 4 hours after 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).

- Participants will be advised to avoid direct sunlight exposure or any high intensity UV light exposure, from admission in Period 1 through the follow-up contact. In addition, participants will be instructed to apply sun cream/lotion with an SPF of ≥50, and wear eye-protective sunglasses as appropriate.

5.4. Screen Failures

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

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products/auxiliary medicinal products, 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-07328948;
- Placebo for PF-07328948.

6.1. Study Intervention(s) Administered

Study Intervention(s)		
Intervention Name	PF-07328948	Placebo
Arm Name (group of participants receiving a specific treatment or no treatment)	PF-07328948	Placebo
Type	Drug	Drug
Dose Formulation	Bulk powder for extemporaneous preparation of oral suspensions	Bulk powder for extemporaneous preparation of oral suspensions
Unit Dose Strength(s)	10-3000 mg	0 mg
Dosage Level(s)	Single ascending doses 10-3000 mg	0 mg
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided by the sponsor	Provided by the sponsor
Packaging and Labeling	Study intervention will be provided as bulk powder for extemporaneous preparation of oral suspensions.	Study intervention will be provided as bulk powder for extemporaneous preparation of oral suspensions.

Study Arm(s)			
Arm Title	Cohort 1	Cohort 2	Cohort 3 (Optional)
Arm Type	Experimental	Experimental	Experimental
Arm Description	Participants will receive up to 4 dose levels of PF-07328948 and up to 2 matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined	Participants will receive up to 4 dose levels of PF-07328948 and up to 2 matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined	Participants will receive up to 4 dose levels of PF-07328948 and up to 2 matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined
Associated Intervention Labels	PF-07328948; Placebo	PF-07328948; Placebo	PF-07328948; Placebo

PF-07328948 and placebo will be provided by Pfizer as bulk powders for extemporaneous preparation of oral suspensions at the CRU.

PF-07328948 and placebo will be presented to the participants in individual dosing containers.

6.1.1. Administration

For fasted period(s):

- Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours) without breakfast on Day 1.

For period(s) when an effect of protein-rich meal (ie, MMTT) is investigated:

- Following an overnight fast of at least 10 hours, participants will be provided a protein-rich meal as 16 ounces of Ensure Plus® breakfast approximately 20 minutes prior to administration of study intervention. The entire Ensure Plus® meal is to be consumed within 10 minutes with study intervention administered approximately 10 minutes after completion of the meal at 0 hour on Day 1 (Section 5.3.2.)

For all periods, investigator site personnel will administer a single oral dose of study intervention on Day 1 of each period with ambient temperature water to a total volume of approximately 240 mL. Administer study intervention according to the EDR.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

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

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

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

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider,

participant, in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

PF-07328948 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 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-07328948 and placebo will be prepared by qualified unblinded site personnel according to the EDR. Blinded study intervention will be administered in a blinded fashion to the participant.

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 (sponsor-unblinded) study.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention.

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 order to maintain this blind, an otherwise uninvolved third party will be responsible for the preparation and dispensing of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense or visual presentation, following randomization or dispensing.

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.

PCRU Pharmacy staff responsible for preparing all study intervention will be unblinded. PCRU site staff 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

As this is a sponsor-open study, a limited number of the sponsor's team members (excluding site staff) may conduct unblinded reviews of the data during the course of the study for the purpose of safety and tolerability assessment, facilitating doseescalation decisions, facilitating PK/PD modeling, and/or supporting clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team.

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

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

6.6. Dose Modification

The decision to proceed to the next dose level of PF-07328948 (either an increase or a decrease) will be made by the study team and the investigator based on safety, tolerability, and preliminary PK data obtained in at least 6 participants (including at least 1 placebo

participant) at the prior dose level. Safety data and PK data through at least 48 hours and 24 hours post-dose, respectively, will be reviewed.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, tolerability, PK, and/or PD findings at a given dose level or to add cohorts to evaluate additional dose levels or repeat dose levels. The study procedures for these additional participant(s)/cohort(s) will be the same as that described for other study participants/cohorts.

6.6.1. Dose Escalation and Stopping Rules

Precautionary sentinel dosing will be used in periods where escalating doses of PF-07328948 will be evaluated and may be omitted when repeating a dose level or administering a lower dose level than previously evaluated. Two participants (1 receiving PF-07328948 and 1 receiving placebo) within a period will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period.

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, ECG, or vital sign abnormalities, in the same organ class, 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 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: Unbound C_{max} of 285 ng/mL; or unbound AUC_{24} of 3250 ng•h/mL.

- If, based on the observed data, the group mean $C_{max,u}$ or $AUC_{24,u}$ 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.

Progression to the next dose level will occur if the last dose level is 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-07328948 greater than 3000 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician 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 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention through the last PK collection, with the exception of moderate/strong CYP3A inducers or time-dependent inhibitors which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Females taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study.

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

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

6.9.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07328948; standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following: adverse events, or some other (administrative) reasons.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for ongoing AEs. See the SoA for data to be collected at the time of

discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

7.1.1. ECG Changes

A participant who meets either of the following 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.

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

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

Differentiating Acute Kidney Injury from Drug-Induced Creatinine Increase:

Both AKI and DICI are associated with

- confirmed Scr increase ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours

  OR

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

AKI is associated with

- simultaneous, confirmed SCys increase and confirmed Scr increase AND decrease in Scr-based eGFR and combined Scr-Scys-based eGFR (where applicable),

  OR

- confirmed albuminuria increase

  OR

- urine volume <0.5mL/kg/h for 6 consecutive hours.

DICI is associated with

- confirmed Scr increase without confirmed increase in reflex SCys

  AND

- confirmed Scr-based eGFR decrease without confirmed combined Scr-Scys-based eGFR decrease (where applicable).

Confirmed post-baseline decrease in kidney function should be assessed individually based on clinical judgment. Cases wherein uncertainty remains, the investigator can review the case with the sponsor. Consult the Kidney Safety Council if such a situation occurs during the study for support if needed.

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results. Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals. If appropriate, nephrology consultation may be recommended to facilitate differentiation of renal parenchymal disease, pre-renal azotemia, and post-renal obstruction. All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

If ≥2 healthy participants in a given period/treatment arm are noted to have confirmed AKI, 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 study procedure;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the participant to comply with the protocol required schedule of study visits or procedures.

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

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

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

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

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study

follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug

shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

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

Any safety, laboratory, or 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 (pulse rate and BP) should be collected prior to the insertion of the catheter.

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

The total blood sampling volume for individual participants in this study is approximately 515-550 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

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

8.2. Efficacy Assessments

No efficacy assessments are being conducted 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

Physical examinations are to be performed at the nominal timepoints specified in the SoA. Additional physical examinations will be permitted, as necessary, to ensure appropriate collection of safety data.

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations (including lung auscultation), lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

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

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

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

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

8.3.2. Neurological Examinations

Neurological examinations as part of the physical exam may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. The neurological exam will consist of assessment of higher cortical function, the cranial nerves, motor function, deep tendon reflexes, sensory exam, and coordination and gait. The exam should be done to the extent needed to assess the participant for any potential changes in neurological status, as determined by the investigator (or designee).

8.3.3. Vital Signs

8.3.3.1. Blood Pressure and Pulse Rate

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements. When triplicate measurements of supine BP or pulse rate are required per SoA, measurements should be collected 2-4 minutes apart.

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

8.3.3.2. Respiratory Rate

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

Additional collection times, or changes to collection times, of vital signs 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.

8.3.4. 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.

Triplicate 12-lead ECGs will be obtained approximately 2-4 minutes apart; the average of the triplicate ECG measurements collected at -1.0, -0.5, and 0 hours pre-dose on Day 1 of each period will serve as each participant's baseline QTcF value for that period.

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 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 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.

For single ECG collections, 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 -4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold

value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

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

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF 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.

8.3.4.1. Continuous Cardiac Monitoring by Telemetry

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

Telemetry should be collected using a centralized system 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 a 2-hour interval before dosing in Period 1. This may be done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the participant is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.

8.3.5. 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 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or 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.

8.4. 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, except as indicated below, after the last administration of the study intervention.

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

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

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

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

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

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has 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.

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A 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 28 days after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

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.

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

Not applicable.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

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

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. Pharmacokinetics

8.5.1. Plasma for Analysis of PF-07328948 Concentrations

Blood samples of approximately 3 mL, to provide approximately 1.2 mL of plasma, will be collected for measurement of plasma concentrations of PF-07328948 into appropriately labeled tubes containing K_2EDTA as specified in the SoA. Instructions for the collection including any potential additive information, processing, aliquoting, handling, storage, and shipment 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. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of PF-07328948. Samples collected for analyses of PF-07328948 plasma concentrations may also be used to evaluate safety aspect related to concerns arising during or after the study, for metabolite identification, and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

CCI [redacted]

Samples collected for measurement of plasma concentrations of PF-07328948 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 may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

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

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 2-mL blood sample optimized for DNA isolation Prep D1.5 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 lab manual and other supporting documentation.

8.7. Pharmacodynamics

Collection of samples for pharmacodynamics research is also part of this study.

The following samples for pharmacodynamics research are required and will be collected from all participants in this study as specified in the SoA.

- Retained Prep B1.5 research sample (Period 1 and Period 4 only);
- Retained Prep B2.5 research sample (Period 1 and Period 4 only);
- CCI [redacted]

[redacted]

8.7.1. Biomarkers

8.7.1.1. Specified Gene Expression (RNA) Research

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

8.7.1.2. Specified Protein Research

Specified protein research is not included in this study.

8.7.1.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.1.4. Retained Research Samples for Biomarker

These Retained Research Samples will be collected in this study:

- 2 mL whole blood Prep B1.5 optimized for plasma (at each sampling time as outlined in the SoA);
- 2 mL whole blood Prep B2.5 optimized for serum (at each sampling time as outlined in the SoA).

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

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 lab manual and other supporting documentation.

8.7.2. Pharmacodynamics Assessments

CCI [redacted]

Instructions for the collection, processing, handling, storage, and shipping 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. This protocol deviation window does not apply to samples

CCI [redacted]

Samples collected for analyses of PD may be used to evaluate safety aspect related to concerns arising during or after the study, for metabolite identification and/or evaluation of bioanalytical method, or for other internal exploratory purposes.

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

CCI [redacted]

The PD samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedures (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.

PD concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

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

CCI [redacted]

8.8. 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.

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 Hypothesis

No formal statistical hypothesis testing will be performed in this study.

9.2. Analysis Sets

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

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

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, secondary and tertiary/exploratory endpoints.

9.3.1. Safety Endpoints

All safety analyses will be performed on the safety analysis set.

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

Medical history and physical examination (including neurological examinations) as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.1.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

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

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 pre-dose triplicate values at -1.0, -0.5, 0 hours pre-dose 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 will be examined. The results of such analyses may not be included in the CSR.

9.3.2. PK Endpoints

The PK concentration and parameter populations are defined in Section 9.2.

9.3.2.1. Derivation of PF-07328948 PK Parameters

The plasma PK parameters for PF-07328948, following oral dose administration, will be derived from the plasma concentration-time profiles as detailed in Table 4, as data permit. In all cases, actual PK sampling times will be used in the derivation of PK parameters.

Table 4. Plasma PF-07328948 PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time curve from time 0 to the time of the C_{last}	Linear/Log trapezoidal method
AUC_{inf}*	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 timepoint estimated from the log-linear regression analysis
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$ *	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F*	Apparent clearance	$Dose/AUC_{inf}$
Vz/F*	Apparent volume of distribution	$Dose/(AUC_{inf}*k_{el})$
AUC_{last}(dn)	Dose-normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf}(dn)*	Dose-normalized AUC_{inf}	AUC_{inf}/Dose
C_{max}(dn)	Dose-normalized C_{max}	C_{max}/Dose

*As data permits.

9.3.2.2. Statistical Methods for PK Data

Plasma concentrations of PF-07328948 will be summarized descriptively by dose (and fasting condition, if appropriate) and nominal PK sampling time. Individual participant and median profiles of the plasma concentration-time data will be plotted by dose (and fasting condition, if appropriate) using actual (for individual) and nominal (for median) times respectively. Median profiles will be presented on both linear and log scales.

The plasma PK parameters will be summarized descriptively by dose (and fasting condition, if appropriate) as applicable. Dose-normalized AUC_{inf}, AUC_{last}, and C_{max} will be plotted against dose (and fasting condition, if appropriate) using a logarithmic scale, and will include individual participant values and the geometric means for each dose. These plots will be used to understand the relationship between the PK parameters and dose (and fasting condition, if appropriate).

If the food effect is assessed, a mixed effects ANOVA will be performed separately on the natural log transformed AUC_{inf}, AUC_{last}, and C_{max} (dose-normalized prior to analysis, if appropriate) with fasting condition included as a fixed effect and participant as a random effect. Further details of this analysis will be provided in the SAP.

Additional PK analyses may be performed if deemed appropriate, and may not be included in the CSR.

9.3.3. Tertiary/Exploratory Endpoint(s) Analysis

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

9.3.4. Other Analyses

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

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. However, as this is a sponsor-open study, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety and tolerability assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9.5. Sample Size Determination

A sample size of approximately 24 healthy adult participants (up to 3 cohorts of approximately 8 participants each) has been chosen based on the need to minimize first exposure to humans of a new chemical entity and the requirement to provide adequate safety, tolerability, PK and PD assessment at each dose level. At each dose level, approximately 6 participants are planned to receive PF-07328948 and approximately 2 participants are planned to receive placebo with all participants at the end of the study having received up to 4 doses of PF-07328948 and up to 2 doses of placebo.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

Not applicable.

10.1.3. 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.

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

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

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

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to 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.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 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.

10.1.7. Data Quality Assurance

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

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

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic 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.

10.1.8. Source Documents

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

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

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.

10.1.9. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, 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.

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

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

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

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

10.1.10. Publication Policy

The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. 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 clinical trial management system.

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.

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 5. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and creatinine eGFR (SCr) Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein SCys[f]	Local dipstick: pH[a] Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[d]	Urine drug screening[b] COVID-19 testing (per CRU procedures) At screening only: • FSH[c] • Hepatitis B surface antigen • Hepatitis B surface antibody[e] • Hepatitis B core antibody • Hepatitis C antibody • Human immunodeficiency virus
If Hb/RBC abnormal: MCV, MCH, MCHC Neutrophils (%) Eosinophils (%) Basophils (%) Lymphocytes (%) Monocytes (%) RBC morphology RBC distribution width	***For suspected DILI:*** AST/ALT Total bilirubin, direct and indirect bilirubin Alkaline phosphatase Total bile acids, GGT Total protein, albumin CK PT, INR Acetaminophen/paracetamol or protein adduct levels Hepatitis serology (even if screening negative) ***For suspected DICI/DIKI:*** Creatinine (SCr) CystatinC (SCys) eGFR (SCr only and combined SCr+SCys) Spot (dipstick) UACR		

Table 5. Protocol-Required Safety Laboratory Assessments

a. Can be performed on dipstick or pH-meter device.
b. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site- and study-specific).
c. For confirmation of postmenopausal status only.
d. Urinary culture only if deemed appropriate by the investigator (eg, if UTI is suspected and/or urine dipstick is positive for nitrites or leukocyte esterase or both).
e. HBsAb will be tested if HBsAg and/or HBcAb is positive
f. Baseline (pre-dose) only

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.

Laboratory/analyte results that could unblind the study and have been collected for the purpose of the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

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

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

10.3.1. Definition of AE

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

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

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

Events NOT Meeting the AE Definition

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

10.3.2. Definition of an SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

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; (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.

- 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.

- 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.

- 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.

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 (refer to the list of highly effective methods below 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 is not pregnant or breastfeeding and is not a WOCBP (see definition in Section 10.4.3).

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt 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 contractive methods are appropriate for this study:

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.

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;

    - Intravaginal;

    - Transdermal.

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

    - Oral;

    - Injectable.

Sexual Abstinence

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

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 study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

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

- The samples will be retained as indicated:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, 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.

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 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

2021 CKD-EPI SCr Only	**SCr** *(mg/dL)*	**SCys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤0.7	NA	$eGFR = 143 \times (SCr/0.7)^{-0.241} \times (0.9938)^{Age}$
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	$eGFR = 135 \times (SCr/0.9)^{-0.544} \times (SCys/0.8)^{-0.778} \times (0.9961)^{Age}$
Source:[9]			

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.[10]

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).

- 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.

10.9. Appendix 9: Protocol Amendment History

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

Amendment 1 (29 September 2022)

Overall Rationale for the Amendment: use precautionary sentinel dosing in dose escalation to mitigate potential unpredicted risks in FIH study

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 (Synopsis), Section 1.2 (Schema), Section 4.1 (Overall Design), Section 6.6.1 (Dose Escalation and Stopping Rules)	Added description wording of precautionary sentinel dosing in Overall Design of synopsis, Schema and Overall Design.	To describe sentinel dosing	Substantial
Section 2.3 (Benefit/Risk Assessment),	Mentioned the use of precautionary sentinel dosing.	To describe sentinel dosing	Substantial
Section 4.2 (Scientific Rationale for Study Design)	Added the scientific rationale for precautionary sentinel dosing.	To provide rationale for precautionary sentinel dosing	Substantial
Title page and Section 1.1 (Synopsis)	Added US IND number	To provide the US IND number	Nonsubstantial

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{24,u}$	unbound AUC over 24 hours
AUEC	area under the effect curve
AV	atrioventricular
Ave	average
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
BCAA	branched-chain amino acid
BCKA	branched-chain ketoacid
BCKDH	branched-chain ketoacid dehydrogenase
BCKDHA	branched-chain ketoacid dehydrogenase E1 subunit alpha
BCRP	breast cancer resistance protein
BDK	branched chain ketoacid dehydrogenase kinase
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C_{ave}	average concentration
CBC	complete blood count
C_{eff}	efficacious concentration
CFR	code of Federal Regulations
CIOMS	council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL	clearance
C_{last}	last quantifiable concentration
C_{max}	maximum concentration
$C_{max,u}$	unbound C_{max}
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
C_p	total concentration

Abbreviation	Term
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced cholestatic injury
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
[redacted]	[redacted]
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECCS	extended clearance classification system
ECG	electrocardiogram or electrocardiography
FDA	Food and Drug Administration
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
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
EP	extemporaneously prepared
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
F	bioavailability
fa	fraction absorbed
fg	fraction escaping intestinal metabolism
FSH	follicle-stimulating hormone
fu	fraction unbound
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
Hb	hemoglobin

Abbreviation	Term
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HF	heart failure
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IADR	idiosyncratic drug reaction
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
Ile	isoleucine
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous(ly)
K	Proportionality constant for Bedside and Modified Schwartz Equations (kidney function)
K_2EDTA	K_2 dipotassium ethylenediaminetetraacetic acid
KDIGO	Kidney Disease Improving Global Outcomes
KIC	ketoleucine
KIV	ketovaline
KMV	ketoisoleucine
LBBB	left bundle branch block
Leu	namely leucine
LFT	liver function test
LVSP	peak left ventricular systolic pressure
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMTT	mixed meal tolerance test
MQI	medically qualified individual
NA	not applicable
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NHP	nonhuman primate

Abbreviation	Term
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OATP	organic-anion-transporting polypeptides
CCI [redacted]	[redacted]
PBPK	physiologically based pharmacokinetic
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
PE	physical examination
PI	principal investigator
PK	pharmacokinetic(s)
PO	by mouth
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
RRCK	Ralph Russ canine kidney
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SCr	serum creatinine
SCys	serum cystatin C
SM	safety margin
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
SRSD	single reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal elimination half-life
T bili	total bilirubin
THC	tetrahydrocannabinol
UACR	urine albumin/creatinine ratio
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States

Abbreviation	Term
UTI	urinary tract infection
UV	ultraviolet
Val	valine
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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