A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, CROSSOVER, FIRST-IN-HUMAN STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE ASCENDING ORAL DOSES OF PF-07853578 ADMINISTERED TO HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07853578
Study Intervention Name:	NA
US IND Number:	165737
EudraCT/EU CT Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5161001
Phase:	1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Learn About the Study Medicine PF-07853578 and How It Acts in the Bodies of Healthy Adults

Document History

Document	Version Date
Amendment 1	06 June 2023
Original protocol	18 April 2023

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 1 (06 June 2023)

Overall Rationale for the Amendment: The protocol is being amended to revise the human exposure stopping limits per FDA feedback. The human exposure stopping limits will be based on total exposures at the NOAEL in dogs in the 2-week GLP toxicity study and will not be corrected for species-dependent protein binding.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
The total C_{max} and total AUC_{24} human exposure stopping limits for PF-07853578 were changed to CCI ng/mL and CCI ng•h/mL, CCI .	FDA requested to set the total human PK exposure limits to the total exposures observed at the NOAEL in the dog.	Section 4.3.3 (Human Exposure Stopping Limits), 4.3.4 (Rationale for Dose Selection), and 6.6.1 (Dose Escalation and Stopping Rules).
Non-substantial Modification(s)		
Updated brief title.	The brief title was updated to be consistent with the brief title on clinicaltrials.gov.	Title page and Section 1.1 (Synopsis)
Changed blood pressure and pulse rate measurements.	Blood pressure and pulse rate measurements were updated per internal guidance to facilitate exposure-response modeling.	Section 1.3 (Schedule of Activities)
Updated the indication of PF-07853578.	Indication of PF-07853578 was updated to be consistent with IND and CDP documents.	Section 1.1 (Synopsis), Section 2 (Introduction), Section 2.3.3 (Overall Benefit/Risk Conclusion)

Description of Change	Brief Rationale	Section # and Name
Removed redundant text regarding interleaving cohort design.	Clarification	Section 4.2 (Scientific Rationale for Study Design)
Clarified text regarding water consumption when dosing under fed condition.	Clarification	Section 5.3.2 (Meals and Dietary Restrictions)
Added text regarding extemporaneous dose preparation.	Clarification	Section 6.2.1 (Preparation and Dispensing)
Removed redundant text regarding physical examination.	Clarification	Section 8.3.1 (Physical Examinations)
Minor grammatical changes.	Clarification	Section 1.1 (Synopsis), Section 4.2 (Scientific Rationale for Study Design), Section 10.7.1 (Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury), Section 10.10 (Appendix 10)

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, Crossover, First-in-Human Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Oral Doses of PF-07853578 Administered to Healthy Adult Participants

Brief Title: A Study to Learn About the Study Medicine PF-07853578 and How It Acts in the Bodies of Healthy Adults

Regulatory Agency Identification Number(s):

US IND Number:	165737
EudraCT/EU CT Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5161001
Phase:	1

Rationale: This study is the first clinical study with PF-07853578. The safety, tolerability, and plasma pharmacokinetics (PK) of PF-07853578 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-07853578 administered orally to healthy adult participants.	• Assessment of AEs, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead ECGs, PEs and neurological examinations.
Secondary:	**Secondary:**
• To evaluate the PK of PF-07853578 following single doses of PF-07853578 administered orally to healthy adult participants.	• PK parameters derived from plasma PF-07853578 concentrations: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}, and $t_{½}$.

Abbreviations: AE = adverse event; AUC_{inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinite; AUC_{last} = area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max} = maximum plasma concentration; ECG = electrocardiogram; PE = physical examination; PK = pharmacokinetic(s); $t_{½}$ = terminal half-life; T_{max} = time for C_{max}.

Overall Design: This study is a randomized, investigator- and participant-blind, sponsor-open, placebo-controlled, first-in-human (FIH), single ascending dose, 4-period, crossover, interleaving design study of PF-07853578 orally administered to healthy adult participants. Precautionary sentinel dosing will be used in this study. Two participants (1 receiving PF-07853578 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. Sentinel dosing may be omitted when repeating a dose level or administering a lower dose level than previously evaluated.

Number of Participants: Approximately 24 healthy adult participants (up to 3 cohorts of approximately 8 participants each) will be enrolled in the study.

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

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

Inclusion Criteria

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

1. Male and female participants of non-childbearing potential aged 18 to 65 years at screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

2. BMI of 16 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

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).

2. Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality 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, with the exception of moderate or strong cytochrome P450 3A (CYP3A) inducers or inhibitors which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention.

4. 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). Participation in

studies of other investigational products (drug or vaccine) at any time during their participation in this study.

5. A positive urine drug test.

6. Screening supine blood pressure (BP) ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of supine rest. If systolic BP is ≥140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

7. Renal impairment as defined by an estimated glomerular filtration rate (eGFR) of <75 mL/min/1.73m². Based upon participant age at screening, eGFR is calculated using the chronic kidney disease epidemiology (CKD-EPI) equations to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events. For eligibility assessment based upon estimated renal function, the higher of the screening and baseline eGFR values may be used.

8. Hematuria as defined by >1+ heme on urine dipstick.

9. Albuminuria as defined by albumin/creatine (Cr) ratio on spot urine albumin (UA) >30 mg/g.

10. 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 atrioventricular (AV) block, or serious bradyarrhythmias or tachyarrhythmias). If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

11. 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:

    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Bilirubin ≥1.05×ULN. Participants with an elevated total bilirubin consistent with Gilbert's Disease may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ upper limit of normal (ULN).

    - Total cholesterol, triglycerides, or direct LDL ≥1.25×ULN.

12. 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).

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

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

Study Arms and Duration: The total duration of participation from the screening visit to the telephone follow-up contact will be approximately 17 weeks for each participant.

Study Intervention(s)		
Intervention Name	PF-07853578	Placebo
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	Bulk powder for extemporaneous preparation of oral solutions and suspensions	Bulk powder for extemporaneous preparation of oral solutions and suspensions
Unit Dose Strength(s)	0.1-500 mg	0 mg
Route of Administration	Oral	Oral

Abbreviations: AxMP = auxiliary medicinal product; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product.

Study Arm(s)			
Arm Title	Cohort 1	Cohort 2	Cohort 3 (Optional)
Arm Description	Participants will receive up to 4 dose levels of PF-07853578 and up to 2 dose levels of matching placebo. Doses will be administered as oral solutions or suspensions as escalating single doses to be determined.	Participants will receive up to 4 dose levels of PF-07853578 and up to 2 dose levels of matching placebo. Doses will be administered as oral solutions or suspensions as escalating single doses to be determined.	Participants will receive up to 4 dose levels of PF-07853578 and up to 2 dose levels of matching placebo. Doses will be administered as oral solutions or suspensions as escalating single doses to be determined.

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

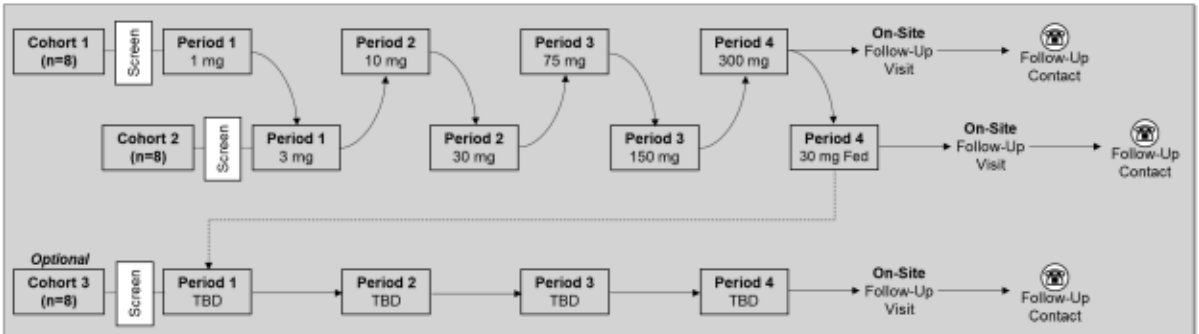
to be up to approximate semi-logarithmic increases in exposure from the previous highest dose level that has been evaluated. The actual dose levels, target exposures, and/or dose level increments may be adjusted during the study based on emerging human safety, tolerability, and PK data, but projected exposures will not exceed the predefined human exposure limits.

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, tolerability, and PK 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-07853578 following oral dose administration will be derived from the plasma concentration-time profiles. Plasma PK parameters and concentrations of PF-07853578 will be descriptively summarized by dose (and fasting condition and formulation, 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 be expected to commit time and may experience some discomfort while undergoing study procedures. However, they will receive close monitoring of their safety via safety monitoring procedures (eg, physical examinations, 12-lead ECGs, vital signs) 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-07853578 in this study as part of the clinical development for the treatment of nonalcoholic steatohepatitis (NASH) with liver fibrosis in patients who are carriers of the PNPLA3-148M allele.

1.2. Schema

Figure 1. Study Design: Interleaving, Placebo-Controlled, 4-Period, Crossover Design



- Each period will consist of admission on Day -1, dosing on Day 1, and discharge at approximately 72 hours post-dose. Within a participant, there will be a washout interval of ≥10 days between doses.
- In each period, 6 participants will be randomized to receive PF-07853578, and 2 participants will be randomized to receive matching placebo.
- Precautionary sentinel dosing will be employed. Two participants (1 receiving PF-07853578 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. Sentinel dosing may be omitted when repeating a dose level or administering a lower dose level than previously evaluated.
- The starting dose level in Period 1 of Cohort 1 is 1 mg. All other planned dose levels in other periods and cohorts may be adjusted pending emerging safety, tolerability, and PK data from previous periods and cohorts.
- Optional exploratory assessments: 1) effect of food on PF-07853578 PK and/or 2) evaluation of PK of an intermediate dosage strength oral solution of PF-07853578.
- Dose escalation to occur following review of PK data through at least 24 hours post-dose and safety and tolerability data through at least 48 hours post-dose of the current period. Cumulative safety and tolerability from all previous periods will also be reviewed.
- On-site follow-up visit to occur on 7-10 days after administration of the final dose of study intervention. Follow-up contact may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.

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 Assessments

Visit Identifier Abbreviations used in this table are in Appendix 10.	Screen	Period 1 to Period 4						Follow-Up		ET	Notes
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1	Day 2		Day 3	Day 4	Visit: Day 8-11	Contact: Day 29-36		Follow-up contact may occur via telephone contact and must occur 28-35 days after the final dose of study intervention.
Hours After Dose			0	24	36	48	72				
Informed consent	X										See Section 10.1.3 for additional information.
Outpatient visit	X							X			7-10 days after the final dose of study intervention (Period 4 only)
Inpatient stay at CRU		X	→	→	→	→	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 (eg, $t_{½}$ is longer than expected) dictate the need to prolong confinement in the CRU.
Discharge from CRU							X				
Demography	X										Including height and weight
Inclusion/exclusion criteria	X	X									Day -1 in Period 1 only. Review any changes from Screening.
Medical/medication history	X	X									Day -1 in Period 1 only. Review any changes from Screening.
History of alcohol, tobacco, and illegal drug use	X	X									Day -1 in Period 1 only. Review any changes from Screening.
Review concomitant treatments	X	→	→	→	→	→	→	→	X	X	See Section 6.9 for additional information.
Contraception check	X	X					X	X	X	X	Contraceptive guidance is outlined in Appendix 4.

Table 1. Study Schedule of Assessments

Visit Identifier Abbreviations used in this table are in Appendix 10.	Screen	Period 1 to Period 4						Follow-Up		ET	Notes
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1	Day 2		Day 3	Day 4	Visit: Day 8-11	Contact: Day 29-36		Follow-up contact may occur via telephone contact and must occur 28-35 days after the final dose of study intervention.
Hours After Dose			0	24	36	48	72				
COVID-19 related measures	X	X	→	→	→	→	X	X		X	Per CRU procedures.
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	X	X	See Section 8.4.3 for follow-up AE and SAE assessments.
Physical examination	X	X					X			X	Complete PE at screening or upon admission for a participant's first period in the study. Otherwise, brief PE performed for findings during previous exam or new/open AEs, at investigator discretion. See Section 8.3.1 for additional details.
Neurological examination		X	See Table 2	X			X			X	Additional exams performed at investigator discretion. See Section 8.3.2 for additional details.
Respiratory rate				X			X				
Supine BP and pulse rate	X			X	X	X	X	X		X	Single supine blood pressure and pulse rate at screening, follow-up visit, and ET. Triplicate supine blood pressure and pulse rate at all other times. See Section 8.3.3 for additional details.
12-Lead ECG	X			X	X	X	X	X		X	Single 12-lead ECG at screening, follow-up visit, and ET. Triplicates at all other times. See Section 8.3.4 for additional details.
Continuous cardiac telemetry		X									Baseline telemetry to be recorded for at least 2 hours prior to the first dose in Period 1 only. 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 participant is awake. Post-dose telemetry will continue for 8 hours after dosing. See Section 8.3.4.1 for additional details.
Blinded study intervention administration											
Standardized meals/snack		X		X	→	→	X				See Section 5.3.2.
Blood samples for:											
Clinical safety lab tests, including lipid panel	X	X		X			X	X		X	Participants to fast for at least 10 hours prior to sample collection for clinical safety lab tests. See Section 5.3.2 for additional details. Day -1 results will be reviewed and confirmed acceptable prior to dosing.
Serum FSH	X										Only for postmenopausal women.

Table 1. Study Schedule of Assessments

Visit Identifier Abbreviations used in this table are in Appendix 10.	Screen	Period 1 to Period 4						Follow-Up		ET	Notes
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1	Day 2		Day 3	Day 4	Visit: Day 8-11	Contact: Day 29-36		Follow-up contact may occur via telephone contact and must occur 28-35 days after the final dose of study intervention.
Hours After Dose			0	24	36	48	72				
HBcAb, HBsAg, HCVAb, HIV testing	X										See Appendix 2: Clinical Laboratory Tests.
Retained Research Sample for Genetics (Prep D1)			X								Prep D1 Retained Research Samples for Genetics: Collected in Period 1 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. To be collected as outlined in Section 8.6.2.
Specified genetics for PNPLA3			X								Collected in Period 1 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. To be collected as outlined in Section 8.6.1.
Retained Research Sample for Biomarkers (Prep B2.5)			See Table 2	X							To be collected as outlined in Section 8.7.4.
PF-07853578 plasma PK				X	X	X	X			X	See Section 8.5 for additional details.
Urine samples for:											
Urine drug testing	X	X									Results of any pre-dose testing to be confirmed acceptable prior to dosing.
Urinalysis (with microscopy, if needed)	X	X		X			X	X		X	

Table 2. Study Schedule of Assessments for PK, Vitals, and ECGs on Day 1 of Each Period

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Period 1 to Period 4**												**Notes**
	Day 1												
Hours Relative to Dosing at 0 hour	**-1.0**	**-0.5**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	Day 1 activities at time = 0 hour are prior to the dose, except for study intervention administration.
Blinded study intervention administration			X										• Precautionary sentinel dosing will be used in any period evaluating escalating doses of PF-07853578. See Section 4.1 for additional details. • Participants should fast for at least 10 hours prior to dosing, except for periods in which food effects are investigated. See Section 5.3.2 for additional information.
Neurological exam							X						Additional exams performed at investigator discretion. See Section 8.3.2 for additional details.
Respiratory rate			X				X			X			
Supine BP and pulse rate			X	X	X	X	X	X	X	X	X	X	Triplicate supine blood pressure and pulse rate at all times. See Section 8.3.3 for additional details.
12-Lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	Triplicate measurements at all timepoints. See Section 8.3.4 for additional details.
Continuous cardiac telemetry			X	→	→	→	→	→	→	X			See Section 8.3.4.1 for additional details.
Standardized meals/snack								X			X		See Section 5.3.2.
Blood sampling for:													
Retained Research Sample for Biomarkers (Prep B2.5)			X				X						To be collected as outlined in Section 8.7.4.
PF-07853578 plasma PK			X	X	X	X	X	X	X	X	X	X	See Section 8.5 for additional information.

2. INTRODUCTION

PF-07853578 is a first-in-class, orally administered, small molecule covalent modifier of PNPLA3 that is currently being developed for the treatment of NASH with liver fibrosis in patients who are carriers of the PNPLA3-148M allele.

2.1. Study Rationale

This study will be the first time PF-07853578 is administered to humans. The purpose of the study is to evaluate the safety, tolerability, and plasma PK of PF-07853578 following administration of escalating, single oral doses to healthy adult participants.

2.2. Background

2.2.1. PNPLA3 and NAFLD/NASH

NAFLD, and the more serious form of the disease NASH, is the most prevalent liver disease in Western countries.[1] It is estimated that 25% of adults in developed countries have NAFLD, and up to 6% have NASH.[2] NAFLD is characterized by excessive accumulation of hepatic lipid (steatosis). A subset of patients with NAFLD progress to NASH, which is defined as the histological presence of hepatic steatosis, inflammation, and hepatocellular injury (hepatocyte ballooning).[3] Some patients with NASH develop progressive hepatic fibrosis, and if left untreated, NASH can progress to life-threatening conditions such as cirrhosis and HCC.[4]

One of the strongest genetic risk factors identified for NAFLD is the rs738409 variant in the PNPLA3 gene which encodes an isoleucine to methionine substitution at amino acid position 148 of the PNPLA3 protein (PNPLA3-148M).[5] The PNPLA3-148M allele is common and found in 23% of the total population with higher frequencies in the Latino population (42%) and lower frequencies among African/African American populations (14%).[6, 7] Carriers of the PNPLA3-148M allele also have a higher risk of NASH, cirrhosis, hepatic decompensation, HCC, and liver-related and all-cause mortality.[8-12]

PNPLA3 is a triglyceride lipase found on lipid droplets. Compared to wildtype PNPLA3 (PNPLA3-WT), the PNPLA3-148M protein has reduced catalytic activity and accumulates on hepatic lipid droplets.[13] The accumulation of PNPLA3-148M protein on hepatic lipid droplets is required in a "gain-of-pathogenic-function" manner to promote NAFLD and NASH in mice, and reductions in PNPLA3-148M protein levels in mice using ASOs, shRNAs, or PROTAC technology reduces hepatic steatosis, inflammation, and fibrosis.[14, 15] PF-07853578 is a potent, orally-bioavailable, small-molecule inhibitor of PNPLA3 that has been demonstrated in nonclinical models to degrade PNPLA3-148M protein and reduce hepatic triglycerides and is postulated to decrease steatosis in PNPLA3-148M carriers with NASH.

2.2.2. Nonclinical Pharmacology

PF-07853578 is an inhibitor of PNPLA3 that irreversibly covalently modifies and degrades the PNPLA3 protein. CCI [redacted]

CCI [redacted] In mice expressing human PNPLA3-148M from a BAC-TG, administration of PF-07853578 dose-dependently reduced PNPLA3-148M protein in liver tissue. PF-07853578 administration also reduced PNPLA3-148M protein accumulation and steatosis in BAC-TG mice that were fed a high sucrose diet to promote PNPLA3-148M protein accumulation and steatosis. Additional details are included in the IB.

2.2.3. Nonclinical Pharmacokinetics and Metabolism

The oral bioavailability of PF-07853578 was variable across nonclinical species ranging from CCI [redacted] at the higher dose in mice. The CL_p in rats was CCI [redacted], but CCI [redacted] in mice, dogs, and monkeys, with CCI [redacted] V_{ss} and a $t_{½}$ of approximately CCI [redacted] or shorter. Following IV administration of PF-07853578 in rats, dogs, and monkeys, the percent of PF-07853578 dose recovered unchanged in urine was CCI [redacted]. Systemic exposure of PF-07853578 in repeat oral dose toxicology studies increased with increasing dose in rats and dogs, however, exposure decreased over the duration of dosing in comparison to Day 1 at the mid and high dose levels in rat and at all doses in dog. There was no evidence of accumulation in either species. Systemic exposure of PF-07853578 was higher in female rats than in male rats at all dose levels, with no sex-related differences in exposure in dogs. In vitro, PF-07853578 was not a substrate for CCI [redacted].

PF-07853578 was similarly highly bound to rat, dog, and human plasma proteins and preferentially distributed into plasma versus blood across the species. PF-07853578 also distributed into the brain in rat after oral dosing.

In vitro metabolite profiling suggests that the primary clearance mechanism for PF-07853578 was CCI [redacted] with no unique human metabolites observed. CCI [redacted] was responsible for a majority of the metabolism of PF-07853578 with minor contributions attributed to CCI [redacted].

Based on FDA and EMA guidances,[16, 17] PF-07853578 has a low risk of eliciting DDI as a result of inhibition of CYP or UGT enzymes but has the potential to elicit CCI [redacted] at the projected efficacious human dose and the dose range planned for the current clinical study. PF-07853578 may perpetrate DDI with CCI [redacted]. In addition, there is a potential for DDIs which could occur with PF-07853578 as a victim if co-administered with moderate and/or potent clinical inhibitors or inducers of CCI [redacted].

Additional details are included in the IB.

2.2.4. CCI [redacted]

CCI [redacted]

2.2.5. Nonclinical Safety

PF-07853578 was evaluated in GLP-compliant repeat-dose general toxicity studies up to 2 weeks in duration in rats and dogs, in vitro and in vivo genetic toxicity studies, and safety pharmacology studies in rats for assessment of neurofunctional and pulmonary effects or dogs for cardiovascular effects.

PF-07853578 was not mutagenic, aneugenic or clastogenic. In the single-dose safety pharmacology studies, CCI [redacted] effects were noted in rats, and a NOEL was established in these studies.

In the 2-week GLP repeat-dose toxicity studies, CCI [redacted]. The NOAELs in the GLP toxicity studies were established at 1000 mg/kg/day in rats and dogs. In rats, the NOAEL corresponded to a total C_{max} of CCI [redacted].

In summary, the nonclinical safety profile of PF-07853578 has been adequately characterized and supports progression into clinical trials of up to 14 days in duration. Additional details of the nonclinical safety program are provided in the IB.

2.3. Benefit/Risk Assessment

Study C5161001 is the first time that PF-07853578 will be administered to humans and is designed primarily to generate safety, tolerability, and PK data for further clinical development. PF-07853578 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-07853578 as a first-in-class therapy for treatment of NASH with liver fibrosis in patients who are carriers of the PNPLA3-148M allele. As of the date of this protocol, no

specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.2.5. The clinical impact of these potential risks will be minimized with precautionary sentinel dosing and through the proposed cautious dose-escalation process wherein higher doses of PF-07853578 will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile. In addition, this study will employ stopping rules for dose escalation (Section 6.6.1) and includes standard, intensive, inpatient monitoring of the participants following dose administration as outlined in the SoA.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07853578 may be found in the IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07853578		
Potential off-target adverse effects	PF-07853578 is a CCI [redacted]. CCI [redacted]. Off-target interactions identified CCI [redacted] may include CCI [redacted] at high concentrations.	• During the study, participants will be in a closely monitored environment while in the CRU. • Human exposures within the planned dose range are projected to all be below concentrations CCI [redacted] • Precautionary sentinel dosing will be used in this study. • Neurologic exams vital signs, ECG chemistries, and fasting lipids will be incorporated as part of safety monitoring. • Smaller dose escalation steps may be implemented if clinically significant safety parameter changes are observed.
Drug-drug interactions resulting in exposure changes of background concomitant medications	At the dose range planned for the current study, PF-07853578 has the potential to elicit CCI [redacted].	• Use of prescription or nonprescription drugs and dietary and herbal supplements will be prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention through the last PK collection.
Drug-drug interactions resulting in PF-07853578 exposure changes	CCI [redacted] was responsible for a majority of the metabolism of PF-07853578 *in vitro*.	• Use of prescription or nonprescription drugs and dietary and herbal supplements that are moderate or strong CCI [redacted] inducers or inhibitors are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention through the last PK collection.
Effects on lipids	CCI [redacted] were seen in 14-day GLP toxicology studies with PF-07853578 in rats and dogs.	• Fasting lipid panels will be included as part of the clinical safety labs.
Effects on ovaries and adrenals	In 14-day GLP toxicology studies with PF-07853578, CCI [redacted] was seen in female rats, and mild-moderate vacuolation of adrenal	• WOCBP will be excluded from the study. • Vital signs and electrolytes in standard clinical safety labs will be performed serially to monitor for signs of adrenal insufficiency.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07853578		
	glands was seen in female and male rats.	
Effects on the liver	Non-adverse increases in liver weight and hepatocyte hypertrophy were seen in rats, and increased ALT in female dogs with PF-07853578 in 14-day GLP toxicology studies.	• Serial liver function tests will be measured as part of standard clinical safety labs.
Effects on pulmonary function	CCI [redacted] were seen in rats with PF-07853578 in single-dose safety pharmacology studies.	• Respiratory rate will be assessed serially as part of safety monitoring.

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, PEs, 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-07853578 in this study as part of the clinical development for the treatment of NASH with liver fibrosis in patients who are carriers of the PNPLA3-148M allele.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of single ascending doses of PF-07853578 administered orally to healthy adult participants.	• Assessment of AEs, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead ECGs, PEs, and neurological examinations.
Secondary:	**Secondary:**
• To evaluate the PK of PF-07853578 following single doses of PF-07853578 administered orally to healthy adult participants.	• PK parameters derived from plasma PF-07853578 concentrations: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf} and $t_{½}$.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To evaluate additional PK parameters of PF-07853578 following single doses of PF-07853578 administered orally to healthy adult participants.	• Additional PK parameters derived from plasma PF-07853578 concentrations: C_{max}(dn), AUC_{last}(dn), and if data permit, AUC_{inf}(dn), CL/F, and V_z/F.
• To evaluate the effect of food on the PK of PF-07853578 following single doses of PF-07853578 administered orally to healthy adult participants (if conducted).	• PK parameters derived from plasma PF-07853578 concentrations after a high-fat/high-calorie meal: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf} and $t_{½}$.
• To evaluate the PK of PF-07853578 following single oral doses of an IDS oral solution of PF-07853578 administered orally to healthy adult participants (if conducted).	• PK parameters derived from plasma PF-07853578 concentrations after IDS oral solution dosing: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf} and $t_{½}$.

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, investigator- and participant-blind, sponsor-open, placebo-controlled, FIH, single ascending dose, 4-period, crossover, interleaving design study of PF-07853578 orally 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 optional third cohort will only be used if the objectives of the study are not fulfilled in Cohort 1 and Cohort 2. Each participant is planned to undergo 4 treatment periods receiving up to 4 doses of PF-07853578 and up to 2 doses of placebo. In

each period, participants will be randomized to either PF-07853578 or placebo in a ratio of 6:2. A diagram of the study design is shown in Figure 1.

Precautionary sentinel dosing will be used in any period evaluating escalating doses of PF-07853578. Two participants (1 receiving PF-07853578 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. Sentinel dosing may be omitted when repeating a dose level or administering a lower dose level than previously evaluated.

Screening activities will be completed over the 28 days prior to randomization in Period 1. In each period, participants will be admitted to the CRU on Day -1 and will remain in the CRU through at least the 72-hour assessments on Day 4. Participants may remain in 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 confinement in the CRU. Participants will receive a single oral dose of PF-07853578 or placebo on Day 1 of each period. Dose levels will be escalated to bracket the expected clinical dose range, but the projected exposures will not exceed the predefined human exposure limits. Within an individual participant, there will be a washout interval of at least 10 days between doses. The total duration of participation from the screening visit to the telephone follow-up contact will be approximately 17 weeks for each participant. Participants will return for an on-site follow-up visit 7-10 days after the final dose of study intervention. The follow-up contact may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.

Dosing will occur in the fasted state for all periods, except if an optional exploratory assessment of the effect of food on PF-07853578 PK is conducted. If the food effect is evaluated, it is anticipated that study intervention will be administered in the fed state in the last period of Cohort 2 or Cohort 3 at a dose level that was previously administered fasted within the same cohort. However, study intervention may be administered in the fed state during any of the study periods/cohorts if thought necessary to achieve study objectives. The actual dose level will be selected based on emerging safety, tolerability, and PK data but will be expected to achieve approximate projected therapeutic exposures (Section 4.3.2).

If evaluated, the IDS oral solution of PF-07853578 is anticipated to be assessed in the last period of Cohort 2 or Cohort 3 at a dose level that was previously administered as a suspension within the same cohort. However, the IDS oral solution may be administered during any of the study periods/cohorts if thought necessary to achieve study objectives.

If a participant drops out before completing all study periods within a cohort or withdraws for a reason unrelated to the safety of the study intervention, 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.

4.2. Scientific Rationale for Study Design

The purpose of this study is to evaluate the safety, tolerability, and PK of orally administered doses of PF-07853578 and placebo in healthy adult males and female participants of non-childbearing potential. Female participants will be confirmed not to be of childbearing potential CCI [redacted], and reproductive toxicity studies with PF-07853578 have not been conducted. In male participants, appropriate measures are expected to be followed to minimize potential transfer of PF-07853578 via semen to partners (see Appendix 4).

Because this is the first time PF-07853578 will be administered to humans, an escalating single, oral dose, crossover interleaving design is planned with careful assessment and ongoing review of safety, tolerability, and PK data of PF-07853578. In each period, 6 participants are planned to receive PF-07853578, and 2 participants are planned to receive placebo. Sentinel dosing will be utilized to ensure that safety and tolerability data in a subset of 2 participants at each dose level supports the testing of additional participants. The crossover design permits both within- and between-participants assessments of safety, tolerability, and PK at multiple dose levels and placebo.

The highest anticipated C_{max} and AUC_{24} of PF-07853578 will not exceed the pre-defined human exposure stopping limits. Furthermore, to permit an unbiased assessment of safety, the administration of both PF-07853578 and placebo in each period will be blind to both site staff (except those involved in preparation of doses) as well as the participants. To permit real-time review of the safety, tolerability, and PK data, a limited number of sponsor study team members will be unblinded.

An interleaving design will be employed in this study to spread PF-07853578 dose levels across a wide range within an individual participant and to reduce the risk of carryover effects on PK and the anticipated dynamics of PNPLA3 levels return to baseline across the planned dose/exposure range. The duration of time between the interleaving dose escalation periods in Cohort 1 and Cohort 2 will be determined by the time required for analysis and review of the safety, tolerability, and PK data from each dosing period before making a decision on the subsequent PF-07853578 dose level to be evaluated. Therefore, the duration of time between doses in an individual participant will be ≥10 days because at high doses of PF-07853578, PNPLA3 levels are predicted to return to baseline in ≤7 days.

Based on the predicted $t_{½}$ of PF-07853578, plasma concentrations of PF-07853578 are expected to be below the limit of detection in approximately 3 days, thus PK samples are planned to be collected over 72 hours post-dose. However, sampling times, duration of sampling, and/or the length of the interval between doses may be modified and/or extended based on emerging PK. The planned doses in the dose escalation sequence (Table 3) 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.

Neurological examinations will be conducted CCI [redacted]. Neurologic signs

will be monitored closely pre- and post-dose, and participants will remain in a closely monitored environment for 72 hours post-dose, which is deemed sufficient based on the predicted effective t½ of PF-07853578.

Respiratory rate will be assessed CCI [redacted].

A fasting lipid panel, consisting of total cholesterol, triglycerides, HDL, and direct LDL, will be monitored with clinical safety lab tests CCI [redacted]

Food may increase PF-07853578 exposures, therefore an exploratory assessment of the effect of food on PF-07853578 PK may be conducted to confirm in silico predictions.

CCI [redacted]

PGx blood samples will be collected for retrospective genotyping of PNPLA3 polymorphism (rs738409) in each participant. This data may enable assessments of differential safety, tolerability, and PK by genotype and may inform the design of subsequent clinical studies with PF-07853578. The results of such analyses are not planned to be included in the CSR.

4.2.1. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of PF-07853578 have not been conducted. 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).

4.3. Justification for Dose

The proposed dose levels of PF-07853578 were derived based on cumulative nonclinical data, including in vitro, in vivo, PK and PD data, and the completed nonclinical toxicity studies. Dose levels have been selected to bracket the expected clinical dose and exposure range, while considering uncertainty in the projected clinically efficacious dose. 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.

4.3.1. Human PK Predictions

PF-07853578 is predicted to have CCI [redacted].

4.3.2. Predicted Efficacious Concentration and Human Dose

The human efficacious dose of PF-07853578 was projected to be CCI [redacted] protein lowering as an CCI [redacted]. The targeted CCI [redacted] [5] and nonclinical data where a CCI [redacted]% reduction in PNPLA3-148M protein levels resulted in a CCI [redacted]% decrease in hepatic triglyceride content in mice expressing the variant protein via a transgene. The dose projection combined predicted human PK parameters in a one-compartment PK model and a dynamic PD model that CCI [redacted] as derived from in vitro studies using human hepatocytes CCI [redacted] risk allele.

The predicted efficacious dose of CCI [redacted].

4.3.3. Human Exposure Stopping Limits

The NOAEL dose levels in the pivotal 2-week GLP toxicity studies were 1000 mg/kg/day (1000 mg/kg QD) in rats and 1000 mg/kg/day (500 mg/kg BID) in dogs, which were the highest doses tested in those respective studies. The observed NOAEL exposures in dogs were lower compared to NOAEL exposures in rats. At the NOAEL in dogs, the total C_{max} and AUC_{24} were CCI [redacted] ng/mL and CCI [redacted] ng•h/mL, CCI [redacted]. Therefore, the human exposure stopping limits for PF-07853578 are:

CCI [redacted]

4.3.4. Rationale for Dose Selection

The safety, tolerability, and plasma PK of PF-07853578 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-07853578 PK. The doses presented in Table 3 are projected based on nonclinical data and may be modified based on emerging observed human safety, tolerability, and PK data generated during this study. The initial range of planned doses in this study were established using toxicokinetic data, predicted human PK parameter estimates, projected PNPLA3 reduction, and projected efficacious concentrations.

Table 3. Predicted Human Exposures, Projected Liver PNPLA3 Reduction, and Safety Margins at Proposed Single Doses of PF-07853578

Dose (mg)	CCI
1	
3	
10	
30	
75	
150	
300	

CCI

A PF-07853578 starting dose level of 1 mg is planned. This starting dose level was informed by CCI and was selected to achieve projected minimal PD activity. At a single dose of 1 mg, PF-07853578 exposures are projected to be well below exposures associated with efficacy and the human exposure limits. CCI are projected to be reduced by approximately CCI, respectively, at C_{max}, suggesting minimal PD activity. The predicted C_{max} and C_{av} are:

CCI

- CCI, below the human exposure limits defined for PF-07853578 dose escalation in Section 4.3.3.

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-07853578 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 approximate 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. Dose levels may also be repeated if warranted.

When the assessment of the effect of food on the PK of PF-07853578 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. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female participants of non-childbearing potential aged 18 to 65 years at screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

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

Other Inclusion Criteria:

2. BMI of 16 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

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

4. Capable of giving signed informed consent as described in 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, HBcAb, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

2. Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality 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, with the exception of moderate or strong CYP3A inducers or inhibitors which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention. (Refer to Section 6.9 for additional details).

Prior/Concurrent Clinical Study Experience:

4. 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). Participation in

studies of other investigational products (drug or vaccine) at any time during their participation in this study.

Diagnostic Assessments:

5. A positive urine drug test.

6. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of supine rest. If systolic BP is ≥140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

7. Renal impairment as defined by an eGFR in adults of <75 mL/min/1.73m². Based upon participant age at screening, eGFR is calculated using the recommended CKD-EPI equations in Section 10.7.2 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events. For eligibility assessment based upon estimated renal function, the higher of the screening and baseline eGFR values may be used.

8. Hematuria as defined by >1+ heme on urine dipstick.

9. Albuminuria as defined by albumin/creatinine ratio on spot urinalysis >30 mg/g.

10. 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 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.

11. 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:

    - ALT, AST, Bilirubin ≥1.05× ULN. Participants with an elevated total bilirubin consistent with Gilbert's Disease may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

    - Total cholesterol, triglycerides, or direct LDL ≥1.25× ULN.

Other Exclusion Criteria:

12. 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).

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

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

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

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

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

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

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 10 hours prior to collection of clinical safety labs and the pre-dose PK sample as indicated on the SoA. Additional unscheduled clinical laboratory measurements should be obtained after the participant has abstained from all food and drink (except water) for

at least 4 hours, except for the fasting lipid panel which should still be obtained after the participant has abstained from all food and drink (except water) for at least 10 hours, unless laboratory measurements are needed more urgently for perceived safety issues.

- Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices (see below) may be consumed with meals and the evening snack.
- Lunch will be provided approximately 4 hours after dosing.
- Dinner will be provided approximately 9 to 10 hours after dosing.
- An evening snack may be permitted.
- On non-dosing days while inpatient, as appropriate, standard morning meal, lunch, and evening meal (along with an evening snack) are to be provided at a similar clock time to the clock time when these meals are offered on the dosing day.
- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.
- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein, with the exception of dosing days in which a high-fat/high-calorie meal will be given prior to study intervention. The daily caloric intake per participant should not exceed approximately 3200 kcal.
- 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.
- Dosing under fed conditions:
    - Following an overnight fast of at least 10 hours, participants should start breakfast approximately 30 minutes prior to administration of study intervention.
    - The breakfast will be consumed over approximately a 20-minute period with study intervention administered approximately 10 minutes after completion of the meal at 0h.

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

- The breakfast will be a high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) meal. The meal will consist of approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories. An example test meal would be: 2 eggs fried in butter, 2 strips of bacon (or 50 g of meat or sausage), 2 slices of toast with butter, 4 ounces (approximately 112 grams) of hash brown potatoes, and 8 fluid ounces (240 mL) of whole milk.

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 of each period during continuous cardiac monitoring, except to use the bathroom. After this, if the equipment setup allows, participants may be ambulatory during the ECG monitoring period, but should not engage in strenuous activities. If equipment does not allow ambulation, appropriate accommodations will be made by the investigator site to facilitate continuous monitoring (eg, bedside urinals should be provided to accommodate participants' excretory needs).

5.4. Screen Failures

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

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

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-07853578;
- Placebo for PF-07853578.

6.1. Study Intervention(s) Administered

Study Intervention(s)		
Intervention Name	PF-07853578	Placebo
Type	Drug	Drug
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	Bulk powder for extemporaneous preparation of oral solutions and suspensions	Bulk powder for extemporaneous preparation of oral solutions and suspensions
Unit Dose Strength(s)	0.1-500 mg	0 mg
Dosage Level(s)	Single ascending doses 0.1-500 mg (see Section 1.2 and Section 4.3.4)	0 mg
Route of Administration	Oral	Oral
Sourcing	Provided by the sponsor	Provided by the sponsor
Packaging and Labeling	Study intervention will be provided in bulk powder for extemporaneous preparation of oral solutions and suspensions. Each container will be labeled as required per country requirement.	Study intervention will be provided in bulk powder for extemporaneous preparation of oral solutions and suspensions. Each container will be labeled as required per country requirement.
SRSD	IB	IB

Study Arm(s)			
Arm Title	Cohort 1	Cohort 2	Cohort 3 (Optional)
Arm Description	Participants will receive up to 4 dose levels of PF-07853578 and up to 2 dose levels of matching placebo. Doses will be administered as oral solutions or suspensions as escalating single doses to be determined.	Participants will receive up to 4 dose levels of PF-07853578 and up to 2 dose levels of matching placebo. Doses will be administered as oral solutions or suspensions as escalating single doses to be determined.	Participants will receive up to 4 dose levels of PF-07853578 and up to 2 dose levels of matching placebo. Doses will be administered as oral solutions or suspensions as escalating single doses to be determined.

PF-07853578 and placebo will be provided by Pfizer [redacted]

- PF-07853578 or placebo low dosage strength oral solutions will be extemporaneously prepared for single oral doses [redacted].
- PF-07853578 or placebo oral suspensions will be extemporaneously prepared for single oral doses [redacted].
- PF-07853578 or placebo [redacted] oral solutions will be extemporaneously prepared for single oral doses [redacted].

PF-07853578 and placebo will be presented to the participants in individual dosing containers.

6.1.1. Administration

For fasted periods:

- Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 08:00 hours (plus or minus 2 hours) without breakfast on Day 1.

For fed period(s):

- Following an overnight fast of at least 10 hours, participants will receive breakfast approximately 30 minutes prior to dosing on Day 1 which is to be completed within approximately 20 minutes as outlined in Section 5.3.2. The participants will then receive study intervention approximately 10 minutes after completion of the meal at approximately 08:00 hours (plus or minus 2 hours).

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. Study intervention will be administered according to the EDR.

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

Following administration of study intervention(s) at the site, participants will be observed for up to 2 hours post-dose by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

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

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

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

8. Further guidance and information for the final disposition of unused study interventions are provided in the CRU 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-07853578 and placebo oral dosing solutions/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-07853578 and placebo will be prepared by qualified unblinded site personnel according to the IPM. 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. This third party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study intervention with the investigator.

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 interventions will be unblinded. PCRU site staff providing technical system support to pharmacy staff and supporting blinded laboratory data processes will be unblinded. These site staff providing system support will not be involved in any data collection or clinic floor activities.

6.4.3. Blinding of the Sponsor

As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation 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. Sensitive Clinical Data

Sensitive clinical data are data collected in this study that have the potential to unblind a participant's treatment assignment. Access to sensitive clinical data will be restricted to authorized individuals until the study has been unblinded. The following data variables are considered sensitive clinical data:

- Study intervention assignments (PF-07853578 or placebo);
- PK data.

6.4.5. Breaking the Blind

The method for breaking the blind in this study will be manual. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to

unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data; and provide information necessary to potentially alter the dose-escalation sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for 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. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will ensure that the study intervention was ingested.

6.6. Dose Modification

The decision to proceed to the next dose level of PF-07853578 (either an increase, decrease, or repeat of a previous dose level) will be made by the study team and the investigator based on safety, tolerability, and preliminary PK data obtained at the prior dose level. At least 6 participants (including at least 1 placebo participant) must complete the prior dose level. PK data through at least 24 hours post-dose and safety and tolerability data through at least 48 hours post-dose of the current period will be reviewed. Cumulative safety and tolerability from all previous periods will also be reviewed.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, tolerability, and/or PK 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.

Precautionary sentinel dosing will be used in this study. Two participants (1 receiving PF-07853578 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. Sentinel dosing may be omitted when repeating a dose level or administering a lower dose level than previously evaluated.

6.6.1. Dose Escalation and Stopping Rules

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

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

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, 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: CCI [redacted].

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

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

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

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

6.8. Treatment of Overdose

For this study, any dose of PF-07853578 greater than 500 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 follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 2 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

PF-07853578 is primarily metabolized by CCI. Therefore, use of prescription or nonprescription drugs and dietary and herbal supplements that are moderate or strong CCI inducers or inhibitors are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention. Use of all other 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.

A non-exhaustive list of excluded moderate or strong CCI inducers or inhibitors is in Appendix 9. Because this is not an all-inclusive list, site staff should consult with the sponsor or designee with any questions regarding potential DDI.

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 HRT 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.

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: AEs or other (administrative) reasons.

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, further study follow-up, and/or future collection of additional information.

7.1.1. Potential Cases of Acute Kidney Injury

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

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

Follow-up Assessments

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

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

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR, eCrCl and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Appendix 7.

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

Differentiating Acute Kidney Injury from DICI

A confirmed Screat increase is defined as:

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

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

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

Adult participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys AND Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.
eGFR	Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available)	

	AKI (including DIKI) **Any one of the below**	**DICI**
Albuminuria or proteinuria	Confirmed albuminuria increase (see Appendix 7 for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

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

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

7.1.2. ECG Changes

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

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

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

7.1.3. 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 should 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 and Baseline Procedures

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

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

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

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

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

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

A participant who qualified for this protocol, completed Day -1 procedures and assessments, and was not dosed as one of the first 2 sentinel participants in a period may be dosed after the study required minimum 24-hour pause without repeating Day -1 procedures and assessments as long as no more than 48 hours separate Day -1 and Day 1. 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 done around the time of a blood draw, ECGs and vital sign assessments (BP and pulse rate) should be collected before the blood draw.

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 400 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

Efficacy parameters are not evaluated in this study.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

A complete PE will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

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

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

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

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

8.3.2. Neurological Examinations

Neurological examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation at the nominal time points specified in the SoA. 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. Additional neurological examinations that are outside of SoA (eg, to evaluate an AE) may be conducted at the discretion of investigator. All neurological exams 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). Changes in the timing or addition of timepoints for the neurological examinations may occur based on emerging data.

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.

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

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

8.3.3.2. 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 BP is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before BP measurement.

8.3.4. Electrocardiograms

Standard 12-lead ECGs will be collected at times specified in the SoA section of this protocol using an ECG system that automatically calculates the HR and measures PR, QT, QTcF, and QRS intervals. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

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 from the current period. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any post-dose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

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 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF

values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

ECG values of potential clinical concern are listed in Appendix 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 2 hours 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 14 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 concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

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

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A 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/participant's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and 28 days after the last dose of study intervention.
- 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 report is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until

completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

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

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

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

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide approximately 1.6 mL of plasma, will be collected for measurement of plasma concentrations of PF-07853578 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual times may change. The actual date and time (24-hour clock time) of each sample will be recorded.

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-07853578. Samples collected for analyses of PF-07853578 plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

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

Samples collected for measurement of plasma concentrations of PF-07853578 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

A 4 mL blood PGx sample for DNA isolation will be collected. DNA samples will be analyzed for the purpose of assessing PNPLA3 polymorphism (rs738409). As part of this analysis, genome-wide markers may be used to control for ethnic-based genetic associations. Additionally, these samples may also be used for retrospective evaluation of additional genetic variants associated with variation in PK, biomarker response, or to explore AEs

should these be observed. Samples will be retained for a period of up to 3 years after the end of the study (eg, CSR finalization).

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

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.

The PGx sample must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PGx processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

As part of further understanding the biological response to study intervention, samples may be used for evaluation of other related genotyping as well as development and validation of bioanalytical methods.

Any data outside of PNPLA3 genotyping will be used for internal exploratory purposes and will not be included in the clinical study report.

8.6.2. Retained Research Samples for Genetics

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

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

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

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.7.1. Specified Gene Expression (RNA) Research

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

8.7.2. Specified Protein Research

Specified protein research is not included in this study.

8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.4. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

- A 4 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.

8.8. 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, or their legally authorized representative's, agreement to participate in a clinical study

Participant Analysis Set	Description
	following completion of the informed consent process and randomization to study intervention.
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. 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.

9.3. Statistical Analyses

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

9.3.1. Safety Analyses

All safety analyses will be performed on the safety population (safety analysis set).

AEs, ECGs, BP, pulse 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 and neurological examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.1.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

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

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, -0.5, and 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-07853578 PK Parameters

The plasma PK parameters for PF-07853578, following oral dose administration, will be derived from the plasma concentration-time profiles using standard noncompartmental methods as detailed in Table 4, as data permit. Actual PK sampling times will be used in the derivation of PK parameters. If actual PK sampling times are not available, nominal PK sampling times will be used in the derivation of PK parameters.

Table 4. Plasma PF-07853578 PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method

Table 4. Plasma PF-07853578 PK Parameters

Parameter	Definition	Method of Determination
AUC_{inf}*	Area under the plasma concentration-time profile 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	$Dose/AUC_{inf}$
V_z/F*	Apparent volume of distribution	$Dose/(AUC_{inf} \cdot k_{el})$
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-07853578 will be listed and summarized descriptively by dose (and fasting condition and formulation, 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 and formulation, 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 and formulation, if appropriate) as applicable. Dose-normalized AUC_{inf}, AUC_{last}, and C_{max} will be plotted against dose (and fasting condition and formulation, if appropriate) using box-and-whisker plots, 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 and formulation, 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.

If the IDS oral solution 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 formulation 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

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

9.4. Interim Analyses

No interim analysis will be conducted for this study.

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, and PK assessment at each dose level. At each dose level, approximately 6 participants are planned to receive PF-07853578 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-07853578 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 SOPs 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 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and IQMP 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 a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

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

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

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

10.1.9. Use of Medical Records

In certain situations, sponsor review of redacted copies of participant medical records for treatment of an AE may be performed, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

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

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

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

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

10.1.10. Study and Site Start and Closure

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

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

The investigator may initiate study-site closure at any time upon notification to the sponsor 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.

10.1.11. 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.

10.1.12. 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 non-study healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week.

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

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. 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 Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV, MCH, MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea Creatinine Cystatin C[a] eGFR[b] Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT, GGT T bili Direct and indirect bilirubin[c] Alkaline phosphatase Uric acid Albumin Total protein Lipid panel: • Total cholesterol • Triglycerides • HDL • LDL (direct)	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[d]	Urine drug screening[f] At screening only: • FSH[e] • HBcAb • HBsAb[g] • HBsAg • HCVAb • HIV • Urine heme[h] • Urine albumin-to-creatinine ratio (quantitative)[i] COVID-19 testing (per CRU procedures)
If Hb/RBC abnormal: Neutrophils (%) Eosinophils (%) Basophils (%) Lymphocytes (%) Monocytes (%) RBC morphology RBC distribution width	**Required:** For suspected DILI: AST/ALT T bili, albumin, CK, direct and indirect bilirubin GGT, PT/INR, eosinophils (%), alkaline phosphatase The following additional testing may be warranted: Acetaminophen/paracetamol or protein adduct levels Hepatitis serology (even if screening negative) Total bile acids Liver imaging For suspected DICI/DIKI: Creatinine (Screat) Cystatin C[a] (Scys) eGFR (Screat only and combined Screat+Scys) Spot (dipstick) UACR		

Table 5. Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other

a. Cystatin C (Scys): Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if Screat increase post-baseline is observed (see Section 7.1.1).
b. Screening and Baseline eGFR is measured with Screat-based formula. Age-specific kidney function calculation (see Section 10.7.2) is recommended to assess presence or absence of post-baseline change in kidney function.
c. Test as reflex if T bili is elevated.
d. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
e. For confirmation of postmenopausal status only in females <60 years old and not using hormonal or HRT only.
f. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site- and study-specific).
g. Test as reflex if HBsAg and/or HBcAb are positive.
h. Assessed by urine dipstick.
i. Assessed by urine dipstick or urine sample biochemical analysis.

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 Meeting the AE Definition

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

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

10.3.2. Definition of an SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
• The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.
g. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

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

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

* **EDP** (with or without an associated SAE): is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form.

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

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

Assessment of Intensity

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

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

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

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

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

Assessment of Causality

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

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

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

SAE Reporting to Pfizer Safety via the CT SAE Report Form

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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 is recommended 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 (a) is not pregnant or breastfeeding; and (b) agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for 28 days; and (c) 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 or oligomenorrhea) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

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

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency (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 + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*

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

    - Oral + barrier*
    - Injectable + barrier*

8. Sexual Abstinence

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

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

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;

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

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:
- Samples for specified genetic analysis (see Section 8.6.1) will be stored for up to 3 years after the completion of this study (eg, CSR finalization).
- 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, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

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

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat-only based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat-only based equation (see Table in Section 10.7.2.1) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat-only based eGFR and combined Screat plus Scys eGFR).

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above) – 2021 CKD-EPI Equations

eGFR (mL/min/1.73m²)[18]

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

10.7.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age-appropriate

formulae (see Section 10.7.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The US National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units for serum creatinine (mg/dL only), Scys (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

10.7.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

KDIGO criteria	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	eGFR ≥90 mL/min/1.73m² OR eCrCl ≥90 mL/min	eGFR ≥60 to 89 mL/min/1.73m² OR eCrCl ≥60 to 89 mL/min	eGFR 30 to 59 mL/min/1.73m² OR eCrCl 30 to 59 mL/min	eGFR 15 to 29 mL/min/1.73m² OR eCrCl 15 to 29 mL/min	eGFR <15 mL/min/1.73m² OR eCrCl <15 mL/min OR dialysis indicated
Albuminuria	Albuminuria <30 mg/g OR <3 mg/mmol	Albuminuria 30 to 300 mg/g OR 3 to 30 mg/mmol	Albuminuria >300 mg/gm OR <3 mg/mmol		

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 ms.
• Absolute value of QTcF > 450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• New-onset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

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

ECG Findings That Qualify as SAEs

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

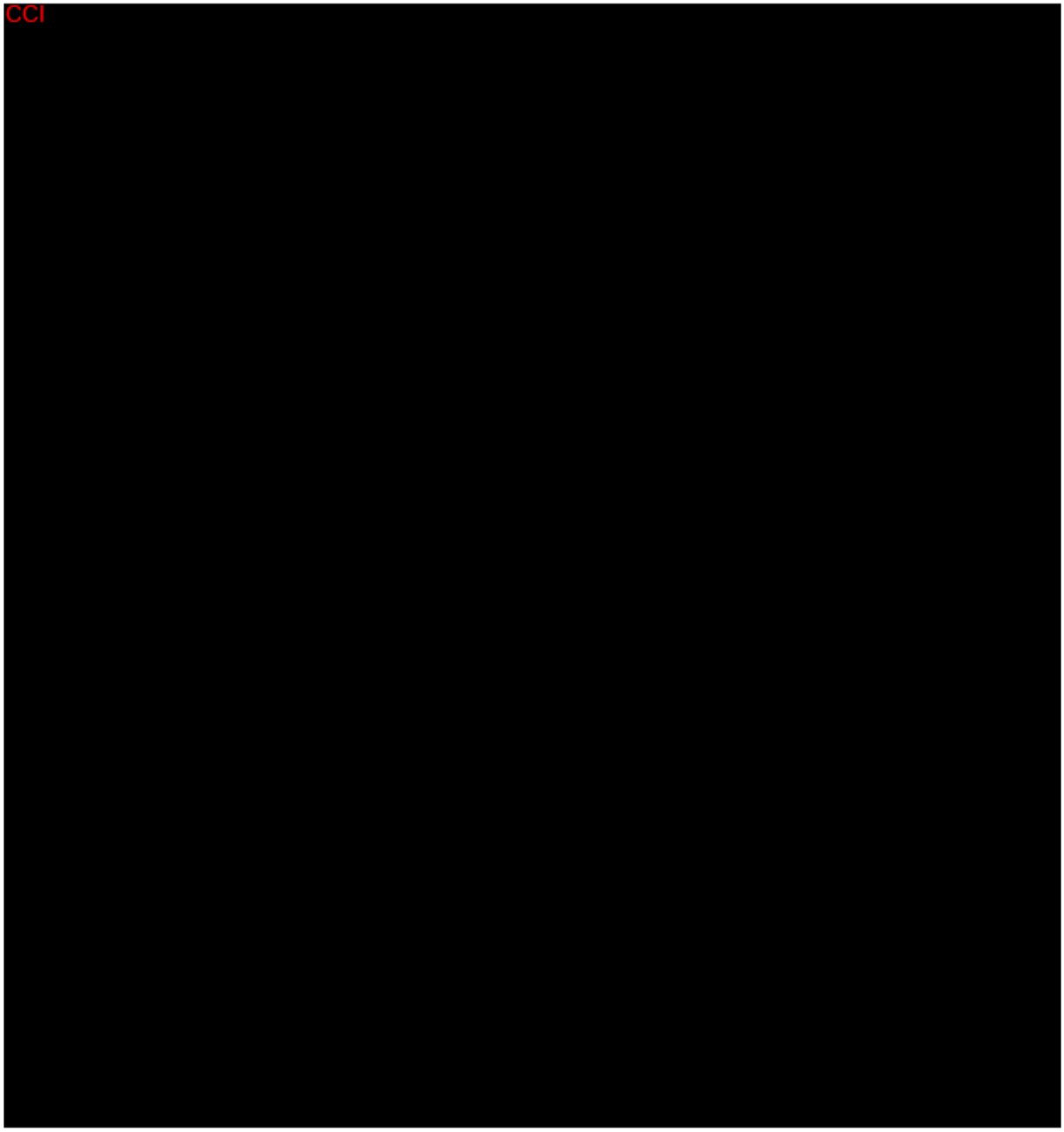
The major events of potential clinical concern listed above are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what is to be reported as AEs/ SAEs.

10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI

PF-07853578 is primarily metabolized by CCI. Therefore, as outlined in Section 5.2 and Section 6.9, use of prescription or nonprescription drugs and dietary and herbal supplements that are moderate or strong CCI inducers or inhibitors are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention.

A non-exhaustive list of excluded moderate or strong CCI inducers or inhibitors is below. Because this is not an all-inclusive list, site staff should consult with the sponsor or designee with any questions regarding potential DDI. The Pfizer study team is to be notified of any prohibited medications taken during the study.

CCI



CCI

[redacted]

This list of drugs prohibited for potential DDI concerns may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs), if the overall benefit:risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
CCI	
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
ANOVA	Analysis of Variance
ASO	antisense oligonucleotides
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinite time
AUC_{inf}(dn)	Dose-normalized AUC_{inf}
AUC_{last}	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_{last}(dn)	Dose-normalized AUC_{last}
AV	atrioventricular
AxMP	auxiliary medicinal product
BAC-TG	bacterial artificial chromosome transgene
BBS	Biospecimen Banking System
CCI	
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
C_{av}	average plasma concentration
CDP	Clinical Development Plan
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
C_{last}	last quantifiable concentration
CL/F	apparent oral clearance
CCI	
CL_p	plasma clearance
C_{max}	maximum plasma concentration
C_{max}(dn)	Dose-normalized C_{max}

Abbreviation	Term
CNS	central nervous system
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
Cr	creatinine
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
CYP3A	cytochrome P450 3A
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
DCT	data collection tool
DDI	drug drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
dn	dose-normalized
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice

Abbreviation	Term
Hb	hemoglobin
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCVAb	hepatitis C antibody
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IDS	intermediate dosage strength
I_{max}	maximum inhibitory effect
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IQMP	integrated quality management plan
IRB	Institutional Review Board
IV	intravenous(ly)
KDIGO	Kidney Disease Improving Global Outcomes
K_{el}	elimination rate constant
LBBB	left bundle branch block
LDL	low-density lipoprotein
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MQI	medically qualified individual
NA	not applicable
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
CCI	
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)

Abbreviation	Term
PE	physical examination
CCI	
PGx	pharmacogenomic
PI	principal investigator
PK	pharmacokinetic(s)
PNPLA3	Patatin-like phospholipase domain-containing protein 3
PNPLA3-148M	isoleucine to methionine substitution at amino acid position 148 of the PNPLA3 protein
PNPLA3-WT	wildtype PNPLA3
CCI	
PROTAC	proteolysis targeting chimera
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
Screat	serum creatinine
Scys	serum cystatin C
shRNA	small hairpin RNA
SoA	Schedule of Activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TBD	to be determined
T bili	total bilirubin
CCI	
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
UA	urine albumin
UACR	urine albumin/creatinine ratio
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
V_{ss}	volume of distribution at steady state

Abbreviation	Term
V_z/F	apparent oral volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WT	wild-type

11. REFERENCES

1. Review T, LaBrecque DR, Abbas Z, et al. World Gastroenterology Organisation global guidelines: Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. J Clin Gastroenterol. 2014;48(6):467-73.
2. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84.
3. Diehl AM, Day C. Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis. N Engl J Med. 2017;377(21):2063-72.
4. Khan FZ, Perumpail RB, Wong RJ, et al. Advances in hepatocellular carcinoma: Nonalcoholic steatohepatitis-related hepatocellular carcinoma. World J Hepatol. 2015;7(18):2155-61.
5. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008;40(12):1461-5.
6. Genome Aggregation Database (gnomAD) v3.1.2 [Available from: https://registry.opendata.aws/broad-gnomad/].
7. Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020;581(7809):434-43.
8. Grimaudo S, Pipitone RM, Pennisi G, et al. Association Between PNPLA3 rs738409 C>G Variant and Liver-Related Outcomes in Patients With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol. 2020;18(4):935-44 e3.
9. Holmer M, Ekstedt M, Nasr P, et al. Effect of common genetic variants on the risk of cirrhosis in non-alcoholic fatty liver disease during 20 years of follow-up. Liver Int. 2022;42(12):2769-80.
10. Liu YL, Patman GL, Leathart JB, et al. Carriage of the PNPLA3 rs738409 C >G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol. 2014;61(1):75-81.
11. Unalp-Arida A, Ruhl CE. Patatin-Like Phospholipase Domain-Containing Protein 3 I148M and Liver Fat and Fibrosis Scores Predict Liver Disease Mortality in the U.S. Population. Hepatology. 2020;71(3):820-34.
12. Dai G, Liu P, Li X, et al. Association between PNPLA3 rs738409 polymorphism and nonalcoholic fatty liver disease (NAFLD) susceptibility and severity: A meta-analysis. Medicine (Baltimore). 2019;98(7):e14324.
13. BasuRay S, Smagris E, Cohen JC, et al. The PNPLA3 variant associated with fatty liver disease (I148M) accumulates on lipid droplets by evading ubiquitylation. Hepatology. 2017;66(4):1111-24.
14. BasuRay S, Wang Y, Smagris E, et al. Accumulation of PNPLA3 on lipid droplets is the basis of associated hepatic steatosis. Proc Natl Acad Sci U S A. 2019;116(19):9521-6.
15. Linden D, Ahnmark A, Pingitore P, et al. Pnpla3 silencing with antisense oligonucleotides ameliorates nonalcoholic steatohepatitis and fibrosis in Pnpla3 I148M knock-in mice. Mol Metab. 2019;22:49-61.
16. In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry: U.S. Food & Drug Administration; 2020 [Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-

documents/in-vitro-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions].
17. Guideline on the investigation of drug interactions: European Medicines Agency; 2013 [Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf].
18. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737-49.