CLINICAL PHARMACOLOGY PROTOCOL

A PHASE 1, 3-PART, SPONSOR OPEN STUDY OF PF-07202954 IN HEALTHY ADULTS: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TO ASSESS SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE (IN PART 1), AND REPEATED (IN PART 2), ESCALATING, ORAL DOSES ALONG WITH CONDITIONAL PART 3 OF RANDOMIZED, OPEN-LABEL ASSESSMENT OF EFFECT OF FOOD ON PF-07202954 EXPOSURE

Study Intervention Number:	PF-07202954
Study Intervention Name:	N/A
US IND Number:	147003
EudraCT Number:	2020-002121-28
Protocol Number:	C4171001
Phase:	1

Short Title: Multi-Part Study in Healthy Adults Evaluating Single- and Repeated-, Escalating, Oral Doses of PF-07202954 Plus Food Effect

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

Amendment 1	01 December 2020	This substantial amendment is making the following changes based on regulatory feedback from the US FDA and FAMHP.
		
		• The PK stopping limit for AUC_{24} are revised to be more conservative:
		
		  • 50% of exposure in male rats at NOAEL in 6 week toxicity study – ie, 18,400 ng•h/mL in Part 1 – refer to Table 1, Table 3, and Section 6.6.1;
		
		  • 10% of exposure in male rats at NOAEL in 6 week toxicity study – ie, 3,680 ng•h/mL in Part 2 with revision to this stopping limit to be considered, via a protocol amendment post formal interim analysis, based on observed data in Part 1 and Part 2 in this study - refer to Number of Participants in Protocol Synopsis, Table 1, Table 4, Section 6.6.1, and Section 9.5.
		
		• Participants with abnormal eGFR, as well as newly added UACR, UPCR will be disqualified – refer to exclusion criterion 7 in Section 5.2, and Table 12.
		
		• Participants will be disqualified based on revised, more conservative limits for ALT and AST (in Part 1 and Part 3) and Total bilirubin (all 3 Parts) – refer to exclusion criterion 7 in Section 5.2.
		
		• CCI [redacted]
		
		• In Part 2, if the observed t½ of PF-07202954 is considerably longer than projected (in Part 1), provisions added that mandate consideration of Day 14

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		PK (along with Day 7) before initiation of dosing in the next cohort – refer to Section 6.6.1. • Added need for eye protection as part of caution for skin sensitivity to light and potential risk for sun burn – refer to Table 1 and Section 5.3.3. • Cross reference to Table 1 added in Section 8.3.8 so as to acknowledge the potential risks based on completed nonclinical toxicity studies (with 1 or more of these potential risks classified as AESIs based on observed data from this study). In addition, the following administrative changes are also being incorporated: • Rationale for dosing with standard meal in Part 1 and Part 2 CCI [redacted] xpanded in Section 4.2.5 and couple of references to substantiate this added. • CCI [redacted] • Definition of baseline, depending on endpoint has different predose nominal collection – note in Table 2 and Table 10 expanded to refer to SAP for definition of baseline for every single endpoint. • CCI [redacted] • Given potential for CYP3A induction, use of estrogen containing hormonal contraception and HRT was not permitted – this intent is clarified in Section 6.5. • While female participants of CBP need to use highly

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		effective method of contraception with low user dependency, in female partners of male participants use of both low user dependent and use dependent options were intended to be permitted given their lower risk – this intent clarified in Section 10.4.1 and Section 10.4.4.
Original protocol	02 October 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: Multi-Part Study in Healthy Adults Evaluating Single- and Repeated-, Escalating, Oral Doses of PF-07202954 Plus Food Effect

Rationale: The current clinical study is the first one proposed with PF-07202954. It is designed as a 3-part study in healthy adults. Part 1 will evaluate the safety, tolerability, and plasma PK CCI with administration of escalating, single, oral doses of PF-07202954 with a standard morning meal. Part 2 will evaluate safety, tolerability, and plasma and urine PK CCI with repeated, escalating doses of PF-07202954 administered once daily with a standard morning meal for 14 days. Based on observed data from Part 1 and Part 2, Part 3 may be conducted to assess the effect of a high-fat/high-caloric meal versus a fasted state on the plasma PK of PF-07202954.

Objectives and Endpoints: The key objectives and endpoints for Part 1, Part 2, and Part 3 (if conducted) of this study are summarized below –

Study	Objectives	Endpoints
Part 1		
Primary	To evaluate ***safety and tolerability*** of ***single***, oral, escalating doses of PF-07202954 administered with a standard morning meal in healthy, adult participants.	Following assessments over ≥10 days of ***each*** Period ***and*** up to Day 30 ±2 days post last dose of study intervention – • AEs; • Clinical laboratory tests; • Vital signs (including BP and pulse rate); • Cardiac conduction intervals via 12-lead ECG.
Secondary	To characterize the ***plasma* PK** profile of PF-07202954 following administration of ***single***, oral, escalating doses.	PK parameters[a] derived from plasma PF-07202954 concentrations: • C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{½}$, *as data permit.*
Part 2		
Primary	To evaluate ***safety and tolerability*** of ***repeated,*** oral, escalating doses of PF-07202954 administered with a standard morning meal in healthy, adult participants with simple hepatic steatosis.	Following assessments over the duration of dosing ***and*** up to Day 30 ±2 days post last dose of study intervention – • AEs; • Clinical laboratory tests; • Vital signs (including BP and pulse rate); • Cardiac conduction intervals via 12-lead ECG.

Secondary	To characterize the ***plasma* and *urine PK*** profiles of PF-07202954 following administration of ***repeated***, oral, escalating doses.	PK parameters[a] derived from plasma PF-07202954 concentrations:
		• Single dose: C_{max}, T_{max}, AUC_{tau} on Day 1;
		• Repeated dose:
		  • Days 7 and 14 – C_{max}, T_{max}, AUC_{tau}, as data permit;
		  • Day 14 – $t_{½}$ as data permit.
		PK parameters[a] derived from urine PF-07202954 concentrations on **Day 14**: Ae_{tau}, Ae_{tau}%, CL_r.

Study	Objectives	Endpoints
Part 3, *if conducted*		
Primary	To characterize the effect of a ***high-fat/high-caloric meal,*** compared to following an overnight fast, on ***plasma PK*** profile of PF-07202954 following administration of a single oral dose to healthy, adults.	PK parameters[a] derived from plasma PF-07202954 concentration: • C_{max}, T_{max}, AUC_{last}, and AUC_{inf}, as data permit.
Secondary	To evaluate ***safety and tolerability*** of a ***single***, oral, dose of PF-07202954 administered with a high-fat/high-caloric meal compared to following an overnight fast.	Following assessments over ≥5 days of ***each*** Period ***and*** up to Day 30 ±2 days post last dose of study intervention – • AEs; • Clinical laboratory tests; • Vital signs (including BP and pulse rate); • Cardiac conduction intervals via 12-lead ECG.

a. For a complete definition of all PK parameters refer to Table 8 and Table 9.

NOTE: For all non-PK related endpoints, ***baseline is defined*** as the time-matched data obtained while on placebo [Part 1], 0H assessment on Day 1 or 0-12H or 0-24H assessment prior to 1st dose [Part 2], ***or*** 0H assessment on Day 1 in *each* Period [Part 3], unless otherwise specified in the SAP.

Overall Design: The study is planned as a 3-part design with investigator- and participant- blinded (sponsor-open), placebo-controlled, randomized, dose-escalation in Part 1 and Part 2; and a randomized, open-label design, in Part 3 (if conducted).

Number of Participants: In this study, participants can be randomized and receive the study intervention in 1 of the 3 parts, *only*. However, participants may be screened for more than 1 part of the study.

Part 1[a]	16 participants (8 per cohort) • 6 active +2 placebo per dose level
Part 2[a]	Initially 30-40 participants with 10 participants per cohort (with potential to expand to 50 [minimum] to 60 [maximum] post formal IA and protocol amendment) • 8 active +2 placebo per cohort
Part 3,[a] if conducted	8 (minimum) to 12 (maximum) participants • Sample size guided by observed variability in plasma PK in Part 1

a. Participants prematurely withdrawn may be replaced at investigator discretion *in consultation* with the sponsor

A total of up to 88 unique participants are planned to be randomized in this study.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process ***and*** *randomization*. Potential participants who are screened for the purpose of determining eligibility for the study, but do *not* participate in the study, are *not* considered "enrolled".

Intervention Groups and Duration: In this study, the study interventions include PF-07202954 and placebo – both as extemporaneously prepared suspensions for oral administration. In Part 1 and Part 3, participants will receive single doses. In Part 2, participants will receive study intervention once daily for 14 days.

DMC or Other Independent Oversight Committee: No

Statistical Methods: The sample size for Part 1 (single, escalating doses) and Part 2 (repeated, escalating doses) 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 and toleration information at each dose level. For Part 3, a range of assumed variability estimates for plasma PK were used to derive the sample size that permits a sufficiently precise assessment with probable 90% CI for an effect size of 1.0 (ie, no change in exposure with and without food).

The data from the three Parts of this study will be analyzed separately and reported in a single CSR. All safety analyses will be performed on the Safety Analysis Set defined as all participants randomly assigned to study intervention and who consume at least 1 dose of study intervention. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

The PK parameters for PF-07202954 following oral dose administration will be derived from the concentration-time profiles. PK parameters and concentrations of PF-07202954 will be descriptively summarized by dose and time, as appropriate.

1.2. Schema

The set-up of each of the 3 Parts of this study are summarized in Figure 1 (Part 1), Figure 2 (Part 2) and Figure 3 (Part 3).

Figure 1. Overall Study Design - Part 1

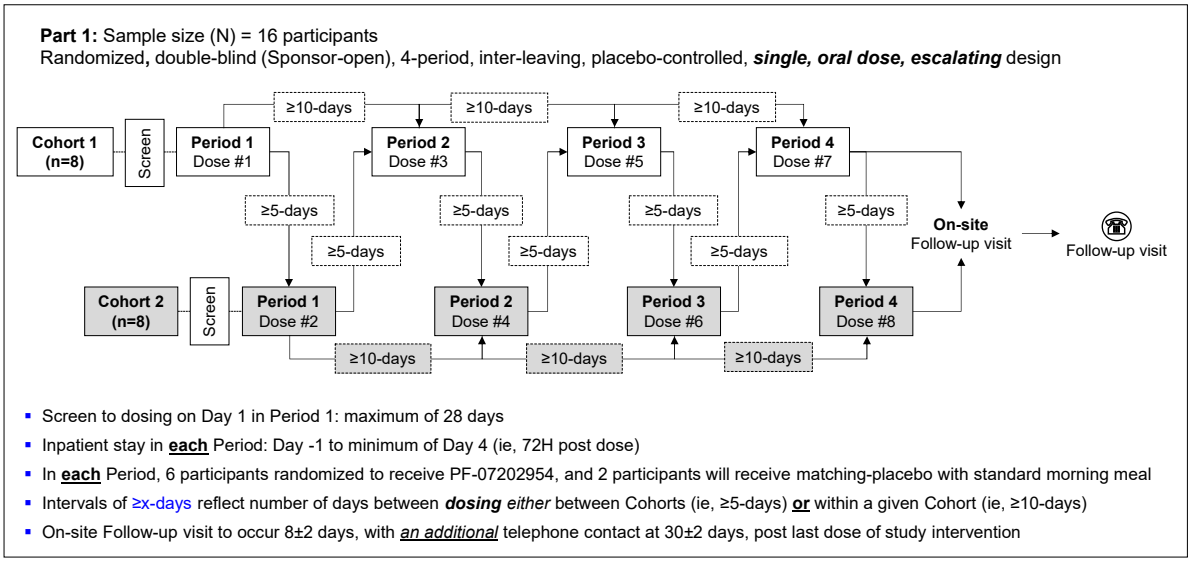


Figure 2. Overall Study Design - Part 2

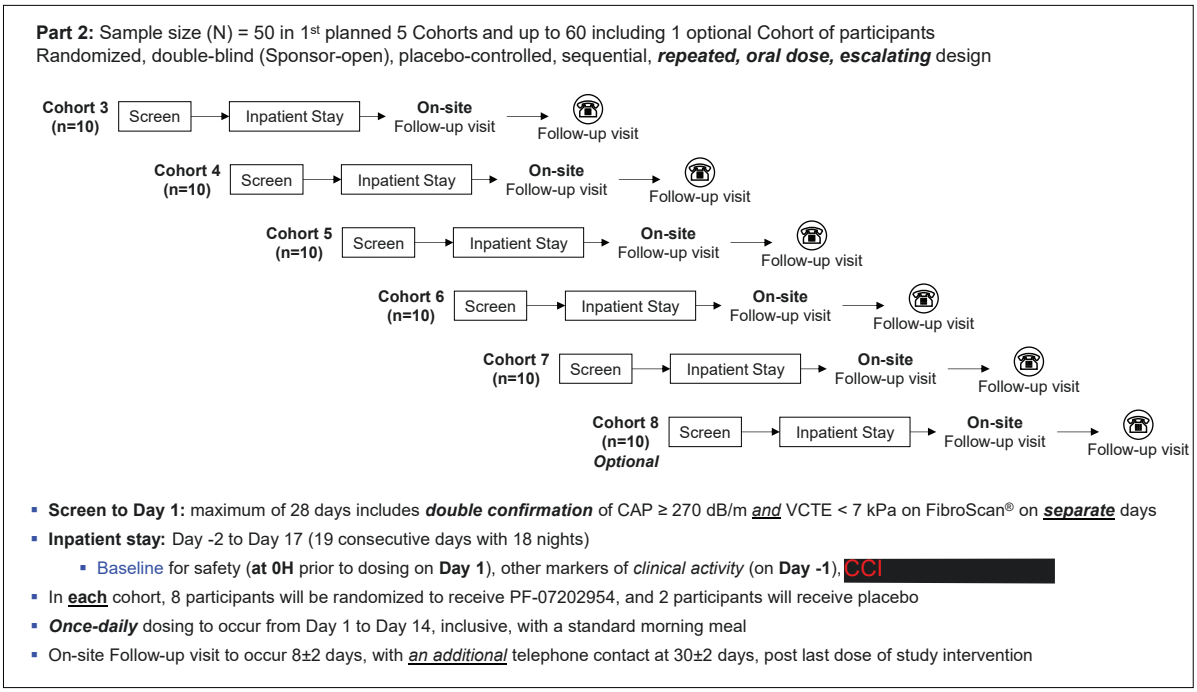
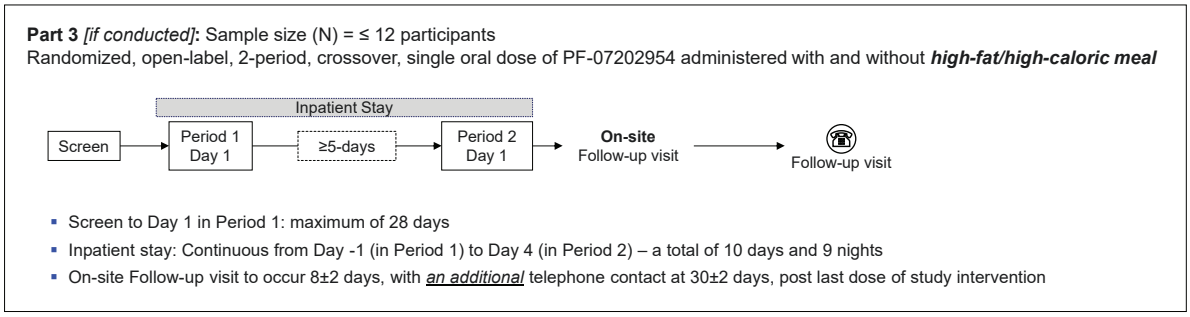


Figure 3. Overall Study Design - Part 3 [if conducted]



1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures; refer to Section 8 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 here, in order to conduct evaluations or assessments required to protect the well-being of the participant.

SoA - TABLE A. Part 1 – Single, Escalating Doses of PF-07202954/Placebo (Cohorts 1 and 2)

[refer to sub-sections in Section 8 for additional details]

Visit Identifier (for list of abbreviations refer to Section 10.8)	**Screen** (≤28 days)	**Periods 1-4** [dosing separated by ≥10 days between Periods]														**Follow-up**		**D/C**
Day Identifier		**-1**	**1**									**2**		**3**	**4**	**8±2 days[a]**	**30±2 days[a]**	
Hours Post Dose		**N/A**	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**8**	**12**	**16**	**24**	**36**	**48**	**72**			
Informed consent & demography	x																	
Outpatient visit	x															x		
Inpatient stay at CRU		x	→	→	→	→	→	→	→	→	→	→	→	→	→	x			
Assessment of eligibility (& update on Day -1 in Period 1, only)	x	x																
Medical history (with update on Day -1 in Period 1, only)	x	x																
PE (plus height & body weight at Screen, only)[b]	x	x																
Review alcohol/tobacco use & contraception use	x	x													x	x	x[c]	x
Review prior or concomitant (non-) drug treatments	x	x														x	x	x
Supine 12-lead ECG[d]	x[d]		x	x	x	x	x	x	x	x	x		x		x	x	x[d]		x[d]
Single, supine vital signs (includes BP and pulse rate at all times)	x		x	x	x	x	x	x	x	x	x		x		x	x	x		x
SAE and AE monitoring	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x	x
Continuous cardiac telemetry monitoring		x[e]	x	→	→	→	→	→	→	x									
Standard meals[f]		x	x						x		x		x	x	x	x			
Blinded study intervention administration			x[g]																
Blood Sampling [refer to Section 8.5 and Section 10.2] for –																			
Clinical laboratory tests (after ≥10 hour fast)	x	x[h]											x			x	x		x
Serum FSH [in females amenorrhoeic ≥12 months, ***only***]	x																		
Serum pregnancy testing [in ***all*** females]	x	x[h]															x		x
CCI [redacted]																			
Pre-specified PGx *and* Banked Prep D1.5 (Period 1 only)			x																
Plasma PK [timepoints may be revised ***prior*** to dosing, if needed]			x	x	x	x	x	x	x	x	x	x	x	x	x	x			x
CCI [redacted]																			
Urine [refer to Section 10.2] for –																			
Spot sample for drug test	x	x[h]																	
Spot sample for urinalysis, UACR, UPCR (+microscopy, *if needed*)	x	x[h]											x			x	x		x
CCI [redacted]																			

a. Onsite Follow-up visit (8±2 days) and Follow-up telephone contact (30±2 days) to occur relative to last dose of investigational product in Period 4.
b. Complete PE at Screen *or* upon admission in Period 1; otherwise, brief PE for findings at previous PE or new/open AEs **only**, at investigator discretion.
c. Confirmation of appropriate contraception use, *only.*
d. ***Single*** ECG at screen, on-site Follow-up visit, and D/C; ***triplicate*** supine 12-lead ECGs at all other timepoints.
e. Baseline telemetry must be captured for ≥2 hours while participant is awake between admission on Day -1 and 0H on Day 1 of Period 1, ***only.***
f. ***Standard*** meals served at approximate clock times matching nominal time 0H, and at 5H, and 12H relative to dosing on Day 1, while inpatient.
g. Following ≥10 hour overnight fast, dosing at approximately 8:00AM (±2H) to occur ***with*** standard morning meal provided ~30 mins prior to dosing at 0H.
h. Results must be reviewed prior to dosing on Day 1 in *each* Period.

SoA - TABLE B. Part 2 – Repeated, Escalating Doses of PF-07202954/Placebo (Cohorts 3, 4, 5, 6, 7, and optional Cohort 8)
[refer to sub-sections in Section 8 for additional details]

Protocol Activity (for list of abbreviations refer to Section 10.8)	**Screen**		***Baseline***		**All at 0H (prior to dosing) unless otherwise specified**														*Off-Drug*			**Follow-up**		**D/C**
Study Day	**-≤28**	**-≤2[a]**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**22±2[b]**	**44±2[b]**	
Informed consent & demography	x			Refer to **SoA - Table C**	Refer to **SoA - Table C**						Refer to **SoA - Table C**							Refer to **SoA - Table C**						
Outpatient visit	x	x																				x		
Inpatient stay at CRU			x			→	→	→	→	→		→	→	→	→	→	→		→	→	x			
Medical history (update)	x		x																			x		
Review alcohol/tobacco use & contraception use	x		x																		x	x		x
Review prior or concomitant (non-) drug treatments	x		x																			x		
PE (includes height at Screen)[c]	x		x																					
Body weight	x							x						x							x	x		
FibroScan® (after ≥4 hour fast)	x	x[a,j]																						
CCI																								
SAE and AE monitoring	x	x	x			→	→	→	→	→		→	→	→	→	→	→		→	→	x	x	x	x
Supine 12-lead ECG[d]	x[d]							x[d]						x[d]							x[d]	x[d]		x[d]
Single, supine vital signs (BP and pulse rate)	x							x[e]						x[e]							x	x		x
Standardized meals[f]			x			x	x	x	x	x		x	x	x	x	x	x		x	x	x			
Blinded study intervention administration[g]						x	x	x	x	x		x	x	x	x	x	x							
Blood sampling [refer to Section 8.5 and Section 10.2] for:																								
Clinical laboratory tests	x[h]	x[a,j]						x[h]						x[h]					x[h]		x[h]	x[h]		x
Serum FSH [females amenorrhoeic ≥12-months, ***only***]	x																							
Serum pregnancy testing (in ***all*** females)	x	x[j]																			x	x		x
Plasma PK[i]								x						x					x[i]	x[i]	x[i]			x
CCI																								
Urine sampling [refer to Section 10.2] for:																								
Urine drug test	x	x[j]																						
Urinalysis *including* microscopy, UACR, UPCR	x	x						x						x					x		x	x		x

a. Separate from 1st Screen visit; can be conducted post ≥4 hour fast on Day -2 with ***double-confirmation*** on FibroScan® + LFTs ***before*** Day -2 CCI .
b. Onsite Follow-up visit (8±2 days; ie, Day 22±2) and Follow-up telephone contact (30±2 days; ie, Day 44±2) to occur relative to last dose of investigational product.
c. Complete PE at Screen *or* upon admission on Day -2; otherwise, brief PE for findings at previous PE or new/open AEs **only**, at investigator discretion.
d. ***Single*** 12-lead ECG at screen, discharge, on-site Follow-up visit, and D/C; ***triplicate*** 12-lead ECGs at 2H (approximately T_{max}) post dose on Days 4 and 10.
e. Includes assessment at 0H ***plus*** an additional assessment at approximately 2H (approximately T_{max}) post dose.
f. ***Standard*** meals served at approximate clock times matching nominal time 0H, and at 5H, and 12H relative to dosing at 0H, each day while inpatient.
g. Following ≥10 hour overnight fast, dosing at approximately 8:00AM (±2H) to occur ***with*** standard morning meal provided ~30 mins prior to dosing at 0H.
h. Collection following ≥10 hour overnight fast.
i. PK samples collected prior to dose; ***in addition***, on Day 15 [24H (**SoA - Table C**), 36H], Day 16 [48H], and Day 17 [72H] relative to dosing at 0H on Day 14.
j. Results for these collections must be reviewed, by investigator ***before*** Day -2 CCI

SoA - TABLE C. Part 2 – Repeated, Escalating Doses of PF-07202954/Placebo (Cohorts 3, 4, 5, 6, 7, and optional Cohort 8) – Days -1, 1, 7, 14 only
[refer to sub-sections in Section 8 for additional details]

Hours Relative to Dosing at 0H[a] (for list of abbreviations refer to Section 10.8)	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**8**	**10**	**12**	**14**	**16**	**24[b]**
Continued inpatient stay at CRU	→	→	→	→	→	→	→	→	→	→	→	→	→
SAE and AE monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→
Body weight (Days 1, 7, 14)	x												
Triplicate, supine 12-lead ECG (Days 1, 7, 14)	x		x	x		x		x		x			x
Single, supine vital signs (includes BP and pulse rate) - Days 1, 7, 14	x		x	x		x		x		x			x
Standard meals[c]	x						x			x			x
Blinded study intervention administration – Days 1, 7, 14[d]	x												
Blood sampling [refer to Section 8.5, Section 8.8, and Section 10.2] for –													
Clinical laboratory tests after ≥10 hour fast – Days 1, 7, 14	x												
Pre-specified PGx *and* Banked Prep D1.5 – for DNA (Day 1, only)	x												
Serum extracellular vesicles (Days 1, 14)	x												
Plasma PK – timepoints may be revised ***prior*** to dosing, if needed – Days 1, 7, 14	x	x	x	x	x	x	x	x		x		x	x
CCI													
Urine sampling [refer to Section 8.5, Section 8.8, and Section 10.2] for –													
Spot collection for urinalysis *including* microscopy, UACR, UPCR – Days 1, 7, 14	x												
Pre-dose ***spot*** urine for PK - Urine blank on Day 1	x												
24-hour interval for PF-07202954 PK (Day 14)	x	→	→	→	→	→	→	→	→	→	→	→	x
CCI													

a. On Day -1, nominal time to approximately match clock time of collection planned on Day 1 to permit time-matched comparison.
b. Equates to D2,0H (on Day 1), D8,0H (on Day 7), and D15,0H (on Day 14) – refer to **Table B** for other procedures on these days.
c. ***Standard*** meal served ~30 mins prior to dosing at 0H ***plus*** at 5H, and 12H relative to approximate clock times matching dosing on Day 1.
d. Following ≥10 hour overnight fast, dosing at approximately 8:00AM (±2H) to occur ***with*** standard morning meal.
e. CCI

SoA - TABLE D. Part 3 (if Conducted) **– Food Effect (Periods 1 & 2, inclusive)** – [refer to sub-sections in Section 8 of additional details**]**

Visit Identifier [for abbreviations refer to Section 10.8]	**Screen** (≤ 28 days)	**Periods 1 and 2** [dosing separated by **≥5 days** between Periods] *Procedures at 0H (prior to dosing) unless otherwise specified*														**Follow-up**		**D/C**
Day Identifier		**-1**	**1**										**2**		**3**	**4**	**8±2 days**[a]	**30±2 days**[a]	
Hours Post Dose		**N/A**	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**8**	**12**	**16**	**24**	**36**	**48**	**72**			
Informed consent & demography	x																		
Outpatient visit	x																x		
Inpatient stay at CRU		x	→	→	→	→	→	→	→	→	→	→	→	→	→	x			
Assessment of eligibility	x	x[b]																	
Medical history	x	x[b]																	
PE (including height & body weight at Screen, only)[c]	x	x[b]														x	x		
Review alcohol/tobacco use & contraception use	x	x[b]														x[b]	x	x[d]	x
Review prior or concomitant (non-) drug treatments	x	x[b]															x	x	x
Single, supine 12-lead ECG	x		x			x[e]										x	x		x
Single, supine vital signs (includes BP and pulse rate)	x		x			x[e]										x	x		x
SAE and AE monitoring	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x	x
Standard meals[f]		x							x		x		x	x	x	x			
High-fat/high-caloric meal			x[g]																
Open-label study intervention administration			x[g]																
Blood Sampling [refer to Section 8.5 and Section 10.2] for –																			
Clinical laboratory tests [after ≥4 hour fast]	x	x[h]											x			x	x		x
Serum FSH [in females amenorrhoeic ≥12-months, ***only***]	x																		
Serum pregnancy testing (in ***all*** females)	x	x[h]														x[b]	x		x
Pre-specified PGx *and* Banked Prep D1.5 (Period 1 only)			x																
Plasma PK [nominal times *may* be revised ***prior*** to P1D1]			x	x	x	x	x	x	x	x	x	x	x	x	x	x			x
Urine Sampling [refer to Section 10.2] for –																			
Urine drug test	x	x[b,h]																	
Urinalysis, UACR, UPCR (and microscopy, *if needed*)	x	x[h]											x			x	x		x

a. On-site Follow-up visit (8±2 days) and Follow-up telephone contact (30±2 days) to occur relative to last dose of study intervention in Period 2.
b. Procedures to be completed upon admission in Period 1; ***plus,*** upon discharge in Period 2, *when denoted*.
c. Complete PE at either Screen *or* upon admission in Period 1; otherwise, brief PE for findings at previous PE or new/open AEs **only**, at investigator discretion.
d. Confirmation of appropriate contraception use, *only.*
e. Collection to occur at T_{max} post dose, as observed in Part 1.
f. Meals served at approximate clock times matching nominal time 0H (on non-dosing days while inpatient), 5H, and 12H relative to dosing on Day 1.
g. Dosing at 8:00AM (±2H) in both Periods; as dictated by randomization scheme, dosing to occur with either high-fat/high-caloric meal (ie, provided ~30 mins prior to dosing at 0H and expected to be completed ~10 mins prior to dosing) ***or*** with water following an overnight fast of ≥10 hours.
h. Results must be reviewed, by investigator, prior to dosing on Day 1.

2. INTRODUCTION

DGATs catalyze the terminal step in TG synthesis, specifically the esterification of a fatty acid with DAG, resulting in the formation of TG.[1] In mammals, 2 structurally unrelated DGAT enzymes (DGAT1 and DGAT2) have been characterized. DGAT1 is highly expressed in the intestine and plays a central role in fat absorption[2] whereas DGAT2 is highly expressed in liver and adipose.[3] DGAT2i is postulated to decrease hepatic TG synthesis and hepatic lipid burden in NAFLD and NASH. Based on observations in nonclinical studies conducted, it is hypothesized that DGAT2i will impact both physiological drivers contributing to NASH via direct inhibition of liver TG synthesis, as well as adaptive responses leading to reduction in hepatic DNL.

PF-07202954 is a potent and selective, orally administered, DGAT2i demonstrating greater than 4500-fold selectivity over related acyltransferases. It is being developed for the treatment of NASH with liver fibrosis.

2.1. Study Rationale

The current clinical study is the first one proposed with PF-07202954. It is designed as a 3-part study in healthy adults. Part 1 will evaluate the safety, tolerability, and plasma PK of PF-07202954 with administration of escalating, single, oral doses of PF-07202954 with a standard morning meal. Part 2 will evaluate safety, tolerability, and plasma and urine PK as well as markers of clinical activity, in adults with simple hepatic steatosis, upon repeated, escalating doses of PF-07202954 administered once daily with a standard morning meal for 14 days. Based on observed data from Part 1 and Part 2, assessment of the effect of a high-fat/high-caloric meal versus a fasted state on the plasma PK of PF-07202954 may be conducted in Part 3.

2.2. Background

The World Gastroenterology Organization has indicated that NAFLD and NASH are now the number one cause of liver disease in Western countries as the prevalence of NAFLD has doubled during last 20 years, while the prevalence of other chronic liver diseases has remained stable or even decreased.[4] NASH is diagnosed clinically by liver biopsy demonstrating steatosis, inflammation, and cytological ballooning of liver hepatocytes, often with varying degrees of fibrosis. NASH progresses with increasing severity of fibrosis, with cirrhosis developing in a subset of patients[5] and a common complication of cirrhosis being HCC.[6] NASH is a subset of NAFLD (defined as presence of ≥5% hepatic steatosis in the absence of other liver disease etiologies) that is associated with increased all-cause mortality, cirrhosis and end-stage liver disease, increased cardiovascular mortality, and increased incidence of both liver-related and non-liver related cancers.[7]

In a meta-analysis, the global prevalence of NAFLD was estimated at 25%, with the prevalence of NASH in the subset with biopsy-proven NAFLD assessed at 59%.[5] The majority of the population with NAFLD has simple steatosis which has, in general, a benign clinical course. A proportion of participants with NAFLD progress to having hepatocellular ballooning and lobular inflammation, taking close to a decade to progress from 1 stage to the

next and 30-40 years to develop cirrhosis; however, a smaller subset of participants progress very rapidly (within 10 years) to liver cirrhosis from NAFLD.[7] Patients with NASH may be asymptomatic or have non-specific symptoms such as fatigue, despite having significant disease on liver biopsy and associated risk for progression to cirrhosis and liver-related mortality. The 5-year (67%) and 10-year (38%) survival rates in patients with NASH is significantly different than in those with NAFLD. The pooled liver-specific and overall mortality incidence rate estimates among those with NAFLD were calculated at 0.8 and 15.4, respectively, per 1,000 person-years. In contrast, amongst the population with NASH, the incidence rate estimates were 11.8 (liver-specific) and 25.6 (overall) mortality.[7]

Elevated rates of hepatic DNL have been reported to be a distinctive characteristic of NAFLD.[8] Clinically, those with elevated liver fat showed a more than 3-fold increase in the rate of hepatic DNL relative to participants with normal liver fat, but no differences between the groups were detected in adipose FFA flux or in production of VLDL from FFAs. Consequently, when comparing the absolute sources of FA incorporated into VLDL-TG, elevated hepatic DNL was the only source significantly increased in participants with high liver fat.[8] Hepatic DGAT2 deficiency reduces diet-induced hepatic steatosis without increasing inflammation or fibrosis in mice.[9] This supports development of DGAT2 inhibitors as a therapeutic strategy for treating NASH with liver fibrosis and preventing downstream consequences.

2.2.1. Nonclinical Pharmacology

PF-07202954 is a potent and selective inhibitor of hDGAT2. By in vitro biochemical assessment of hDGAT2, PF-07202954 inhibits hDGAT2 with an IC_{50} of 10.1 nM. The selectivity of PF-07202954 for DGAT2 was supported by in vitro studies demonstrating >4500-fold selectivity by biochemical assessment versus related acyltransferases including recombinant hDGAT1, hMGAT2, and hMGAT3, as well as mouse MGAT1. In primary cultures of human hepatocytes, PF-07202954 exhibits an IC_{50} of 11.4 nM for inhibition of hDGAT2. PF-07202954 also inhibits DGAT2 within rat and nonhuman primate primary hepatocytes, yielding IC_{50} of 114 nM and 35.4 nM, respectively.

In vivo, following single dose administration, PF-07202954 demonstrates robust, dose- dependent reduction of plasma and hepatic triacylglycerol in rats fed a sucrose diet. In longer term studies in Western diet fed rats, PF-07202954 also reduces both plasma triacylglycerol and hepatic lipid accumulation. In line with the proposed mechanism of action, PF-07202954 dosing in both sucrose and Western diet fed rats results in suppression of key genes involved in hepatic lipid metabolism, including mRNA expression of Pcsk9. In these nonclinical models dosed with PF-07202954, Pcsk9 mRNA was decreased relative to vehicle treated animals by 64% and 75% in the Western and sucrose diet models, respectively.

2.2.2. Nonclinical PK and Metabolism

Single-dose PK studies with PF-07202954 were conducted after IV administration in rats, dogs, and monkeys and oral administration in rats and monkeys. PF-07202954 demonstrates incomplete oral absorption with mean F of 4% in rats and 21% in monkeys. PF-07202954 exhibited moderate to high CL_{plasma} and moderate V_{ss} in rats, dogs, and monkeys, resulting in a short terminal elimination $t_{½}$ of ≤1.5 hours. Systemic exposure of PF-07202954 as measured by C_{max} and AUC_{24} in repeat oral dose toxicity studies increased with increasing dose in rats and monkeys with evidence of some accumulation in both species. Systemic exposure of PF-07202954 was higher in female rats than in male rats, where sex-related differences were not observed in monkeys. In vitro, PF-07202954 showed moderate passive permeability and preliminary studies indicated that PF-07202954 was a substrate for MDR1 (also known as P-gp) and BCRP efflux transporters.

Following IV administration of PF-07202954, the percent of PF-07202954 dose recovered unchanged in urine was 12% (rat), 25% (dogs), and 2.0% (monkeys). The renal clearance estimates exceed GFR by ~2-fold indicating a net active renal elimination process in rats and dogs but not in monkeys. PF-07202954 is a substrate for the human OAT3 but not OCT1 or OCT2. PF-07202954 was moderately bound to plasma proteins with f_u of PF-07202954 in plasma being 0.422 (rat), 0.531 (dog), 0.370 (monkey), and 0.382 (human). The blood-to-plasma ratios of PF-07202954 in rat, dog, monkey, and human suggest that PF-07202954 does not preferentially distribute into plasma versus red blood cells.

In vitro metabolite profiling in mouse, rat, rabbit, monkey, and human matrices and rat and monkey plasma, suggests that the primary metabolic clearance mechanism for PF-07202954 was oxidation with no unique human metabolites observed. Reaction phenotyping in human hepatocytes indicated CYP3A (>87%) was primarily responsible for the oxidative metabolism of PF-07202954 with minor contributions from CYP2C9 and CYP2C19. However, in humans, metabolic CL of PF-07202954 is projected to account for approximately 40% of total CL, with the remaining 60% as renal CL. Modeling suggests a low risk of clinical DDI with PF-07202954 as a victim upon coadministration with CYP3A4 inhibitors or inducers. As OAT3 is predicted to contribute to the active renal secretion of PF-07202954 in humans, a potential risk of clinical DDI with PF-07202954 as a victim is anticipated upon coadministration with potent inhibitors of OAT3. At the projected effective human dose of 80 mg once daily, PF-07202954 has a low risk of eliciting DDI as a result of inhibition or induction of CYP enzymes or efflux and uptake transporters with the exception of direct inhibition of MATE1 and intestinal BCRP.

2.2.3. Biopharmaceutics

PF-07202954 is a weak base with pKa values of 7.5 and 2.5, thus exhibiting a strong pH-dependent change in solubility. It has high thermodynamic aqueous solubility at physiological pH. The solubility of PF-07202954 in simulated gastric fluid (pH 2.7) and unbuffered water (pH 8) is >27 mg/mL and 0.13 mg/mL, respectively. Solubility in simulated fasted and fed state intestinal fluids (pH 6.9 under both conditions) was observed to be 0.7 mg/mL and 1.2 mg/mL, respectively. Solubility of PF-07202954 is high relative to

the predicted clinical FIH dose range, thus the risk for solubility/dissolution-limited absorption and exposure-limiting precipitation is perceived to be low. Food is expected to have minimal impact on PF-07202954 PK – refer to Section 4.2.5. Preliminary in vitro studies suggest PF-07202954 exhibits moderate in vitro permeability and is a substrate for the intestinal efflux transporters (P-gp and BCRP) that could potentially lead to non-linear plasma PK and high variability in exposure at lower doses.

2.2.4. Nonclinical Safety

PF-07202954 was evaluated in safety pharmacology studies, genetic toxicology studies, and repeat dose toxicity studies, of up to 6 weeks in duration, in rats and cynomolgus monkeys. Target organs in safety pharmacology and general toxicity studies included the CNS (convulsion), kidney/urinary system (degenerative/inflammatory process with evidence of altered renal function), and the CV system (increased QT and QTc-interval). Other key findings included nonadverse hematology changes and nonadverse findings in the gastrointestinal system. The highest NOEL for convulsion was 300 mg/kg which corresponded to total C_{max} of 39,000 ng/mL. The NOEL for QTc-interval changes was 30 mg/kg and corresponded to total C_{max} of 2770 ng/mL. The NOAEL in the 6-week pivotal toxicity studies were 300 mg/kg/day (in rats) and 100 mg/kg/day (in monkeys). In rats, the NOAEL corresponded to a total C_{max} of 6570 (in males) and 14,400 (in females) ng/mL and total AUC_{24} of 36,800 (males) and 89,100 (females) ng•h/mL. In monkeys, the NOAEL corresponded to a total C_{max} of 14,500 ng/mL and total AUC_{24} of 88,500 ng•h/mL.

PF-07202954 was not genotoxic. PF-07202954 may have potential risk for phototoxicity based on its UV absorption profile and will be evaluated for phototoxicity during exploratory development prior to enrollment in Phase 3 clinical studies. Further details of the nonclinical safety program are provided in the current IB.

2.3. Benefit/Risk Assessment

This study is the first time that PF-07202954 will be administered to humans. For healthy participants participating in this 3-part study, no clinical benefit is expected. The purpose of the study is to provide the basis for further clinical development of PF-07202954 as a potential new pharmacological agent for the treatment of participants with NASH with liver fibrosis. As of the issuance of this protocol, no specific human risks have been identified; potential risks based on nonclinical studies are summarized in Table 1. The clinical impact of these potential risks will be minimized through the proposed cautious dose-escalation process wherein higher doses of both single- and repeated-oral doses of PF-07202954 will be administered only after lower doses have been found to be safe and well tolerated in this study and the a priori identified PK stopping limits will not be exceeded (refer to Section 6.6.1). In addition, this study includes standard, intensive inpatient monitoring of the participants following administration of single- and repeated-, escalating, oral doses of the study intervention.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-07202954 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Table 1. Potential Risks with PF-07202954 and C4171001 Design

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Study Intervention – PF-07202954		

Decrease in renal function	• In a 6 week toxicity study ***in rats***, renal tubular degenerative/inflammatory process with a pattern consistent with obstructive nephropathy - associated with evidence of altered renal function and lower urinary tract alterations *without* accompanying changes in SCr and BUN observed at the highest dose tested (1000 mg/kg/day) with most conservative total AUC_{24} (in male rats) of 210000 ng•h/mL.	• Risk communicated through the IB;
		• Heightened surveillance for potential case of acute kidney injury outlined in Section 7.1.2;
		• PK stopping total AUC_{24} criterion set at ***≥200-fold lower*** exposures – refer to Section 6.6.1;
		• Design features ***added*** including –
		  • Enrollment limited to those with ***normal*** renal function as defined by eGFR cut-offs using CKD-EPI formulae, and normal UACR and UPCR – refer to exclusion criterion #7 in Section 5.2;
		  • Conduct of UACR, UPCR at ***all*** timepoints that urinalysis is undertaken following single and repeated dosing
		  • Conduct of urine microscopy at ***all*** timepoints that urinalysis is undertaken following repeated dosing (in Part 2);
		  • CCI [redacted]

Delayed cardiac repolarization	Increase QT and QTc observed in GLP CV study in monkeys at 14400 ng/mL (total C_{max}).	• Risk communicated through the IB; • Serial assessment of triplicate, 12-lead ECGs following single- and repeated- doses of study intervention (Section 8.2.3) along with continuous telemetry following single doses (Section 8.2.3.1); • PK stopping total C_{max} criterion set at close to ***10-fold lower*** (1450 ng/mL) – refer to Section 6.6.1.
Convulsions	Convulsions noted in 1 monkey dosed 500 mg/kg/day where total C_{max} was 46000 ng/mL.	• Risk communicated through the IB; • PK stopping total C_{max} criterion set at ***the conservative 1/10th exposure at NOAEL*** in 6 week GLP monkey study (1450 ng/mL) – refer to Section 6.6.1; • As designed, participants will be under closely monitored environment for ≥72 hours post (last) dose.

Table 1. Potential Risks with PF-07202954 and C4171001 Design

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Skin sensitivity to light; sunburn	Based on UV absorption profiles, PF-07202954 carries risk for phototoxicity.	Standard precaution as it relates to exposure to sunlight/high intensity UV light exposure including eye protection is proposed – refer to Section 5.3.3.
Exposure in utero	To date, EFD studies with PF-07202954 have ***not*** been conducted: • And PF-07202954 is ***not*** mutagenic, clastogenic or aneugenic in in vitro studies ***plus*** was negative in an in vivo rat micronucleus study.	• Risk communicated through the IB; • Enrollment of WOCBP restricted to those using effective contraception – refer to Section 5.3.4 and Section 10.4: • As a measure of caution, serum pregnancy testing undertaken in ***all*** females. • In males who are sexually active with a female partner of childbearing potential, use of barrier methods required/mandated – refer to Section 5.3.4 and Section 10.4.
DDIs resulting in change in exposure of background/concomitant medications	*In vitro* data indicate PF-07202954, at high doses, may be a CYP3A inducer.	• Enrollment of WOCBP restricted to those using effective contraception (with restrictions on use of ***some*** hormonal methods) – refer to Section 5.3.4 and Section 10.4; • CCI [redacted]
	In vitro data indicate PF-07202954 is an inhibitor of MATE1, a renal transporter involved in tubular secretion of organic cations.	CCI [redacted]
Study Procedures		
In Part 1 and Part 2, number of ***serial and parallel*** procedures carry risks for non-evaluable data	• Planned safety and PK evaluation is standard for FIH studies in healthy participants; • ***But*** addition of parallel, multiple, clinical activity parameters done to enable more robust exposure:response characterization.	• At ***selected*** timepoints where evaluation of safety, PK, and clinical activity *is planned in parallel*, doability of all procedures is precedented at sites selected for this study; CCI [redacted]

Table 1. Potential Risks with PF-07202954 and C4171001 Design

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
In Part 2, conduct of different imaging assessments of liver fat during study (ie, quantitative ultrasound-based FibroScan® CCI [redacted]	Procedures are relatively safe; potential risk for non-evaluable images include: • Too much motion, for example, due to increased anxiety, claustrophobia; • Ferric implants/devices, paramagnetic objects within/on body, ferric-containing tattoos in area of interest (abdomen, chest, arms); • Minimum duration of a priori fast *not* followed.	• Permitting pre-procedure use of *short-acting* anxiolytics to manage anxiety CCI [redacted] • Excluding participants if they have contraindications for MRI, or quantitative ultrasound-based assessments (FibroScan®); • Clear communication via ICD of preparation for each visit *including* duration of fast before procedures/visits.
In Part 1 and Part 2, dosing of study intervention with standard meal changes PF-07202954 exposure	In vitro data indicate that PF-07202954 has moderate passive permeability (RRCK=2.9 x 10^{-6} cm/sec), higher solubility at lower pH – refer to Section 2.2.3.	• In Part 1 and Part 2, dosing with a standard (*not* high-fat/high-caloric) meal is proposed to permit assessment of clinical activity – CCI [redacted] – refer to Section 4.2.5; • Dose range evaluated is envisioned to be adjusted based on observed plasma PK while following dose-escalation principles – refer to Section 6.6.1.
Other Factors Potentially Impacting Study Results		
In Part 2, baseline liver fat CCI [redacted] too low hence potentially not permitting assessment of primary pharmacology (ie, liver fat reduction)	Population eligible is healthy with evidence of simple hepatic steatosis assessed using quantitative ultrasound at Screen.	***In Part 2,*** study requires *double-confirmation* of assessment of liver fat (via CAP™ using FibroScan®) and lack of overt liver inflammation/fibrosis (via VCTE™ using FibroScan®) with eligibility required to be met prior to Baseline CCI [redacted]; • CAP™ ≥270 dB/m when assessed on *2 different days* permits >90% probability of liver fat being ≥6% liver fat on baseline CCI [redacted]; • VCTE <7.0 kPa when assessed on *2 different days* being highly suggestive of lack of clinically significant inflammation/fibrosis.[10]

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, PE, 12-lead ECGs, vital signs) which will occur as outlined in this protocol.

In **Part 1**, all participants will receive single, oral, escalating doses of PF-07202954 *and* placebo. Those enrolled in **Part 2** will be randomized to placebo (1 in every 5 participants) *or* repeated, oral, escalating doses of PF-07202954 (4 in every 5 participants). In **Part 3**, if conducted, all participants will receive a single, oral dose of PF-07202954 following an overnight fast *and* with a high-fat/high-caloric morning meal.

2.3.3. Overall Benefit/Risk Conclusion

In consideration of the available nonclinical data and the measures taken to minimize risk to participants in this study, the overall benefit:risk profile for PF-07202954 supports initial clinical development for NASH with liver fibrosis.

3. OBJECTIVES AND ENDPOINTS

Table 2 outlines the key objectives and endpoints for Part 1, Part 2, and Part 3 (if conducted) of this study.

Table 2. Key Objectives and Endpoints in Study C4171001

Study	Objectives	Endpoints
Part 1		
Primary	To evaluate ***safety and tolerability*** of ***single***, oral, escalating doses of PF-07202954 administered with a standard morning meal in healthy, adult participants.	Following assessments over ≥10 days of ***each*** Period ***and*** up to Day 30 ±2 days post last dose of study intervention – • AEs; • Clinical laboratory tests; • Vital signs (including BP and pulse rate); • Cardiac conduction intervals via 12-lead ECG.
Secondary	To characterize the ***plasma* PK** profile of PF-07202954 following administration of ***single***, oral, escalating doses.	PK parameters[a] derived from plasma PF-07202954 concentrations: • C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{½}$, *as data permit.*
Part 2		
Primary	To evaluate ***safety and tolerability*** of ***repeated,*** oral, escalating doses of PF-07202954 administered with a standard morning meal in healthy, adult participants with simple hepatic steatosis.	Following assessments over the duration of dosing ***and*** up to Day 30 ±2 days post last dose of study intervention – • AEs; • Clinical laboratory tests; • Vital signs (including BP and pulse rate); • Cardiac conduction intervals via 12-lead ECG.
Secondary	To characterize the ***plasma* and *urine PK*** profiles of PF-07202954 following administration of ***repeated***, oral, escalating doses.	PK parameters[a] derived from plasma PF-07202954 concentrations: • Single dose: C_{max}, T_{max}, AUC_{tau} on Day 1.

Table 2. Key Objectives and Endpoints in Study C4171001

Study	Objectives	Endpoints

		• Repeated dose:
		  • Days 7 and 14 – C_{max}, T_{max}, AUC_{tau}, as data permit.
		  • Day 14 – $t_{½}$ as data permit.
		PK parameters[a] derived from urine PF-07202954 concentrations on **Day 14**: Ae_{tau}, Ae_{tau}%, CL_r.

Part 3, *if conducted*		
Primary	To characterize the effect of a ***high-fat/high-caloric meal,*** compared to following an overnight fast, on ***plasma PK*** profile of PF-07202954 following administration of a single oral dose to healthy, adults.	PK parameters[a] derived from plasma PF-07202954 concentration: • C_{max}, T_{max}, AUC_{last}, and AUC_{inf}, as data permit.
Secondary	To evaluate ***safety and tolerability*** of a ***single***, oral, dose of PF-07202954 administered with a high-fat/high-caloric meal compared to following an overnight fast.	Following assessments over ≥5 days of ***each*** Period ***and*** up to Day 30 ±2 days post last dose of study intervention – • AEs; • Clinical laboratory tests; • Vital signs (including BP and pulse rate); • Cardiac conduction intervals via 12-lead ECG.

a. For a complete definition of all PK parameters refer to Table 8 and Table 9.

NOTE: For all non-PK related endpoints, ***baseline is defined*** as the time-matched data obtained while on placebo [Part 1], 0H assessment on Day 1 or 0-12H or 0-24H assessment prior to 1st dose [Part 2], ***or*** 0H assessment on Day 1 in *each* Period [Part 3], unless otherwise specified in the SAP.

[redacted]

4. STUDY DESIGN

4.1. Overall Design

The study is planned as a 3-part design with investigator- and participant-blinded (sponsor-open), placebo-controlled, randomized, dose-escalation in Part 1 and Part 2; and a randomized, open-label design, in Part 3 (if conducted). Participants will receive oral dose(s) of PF-07202954 and/or placebo in this study. A total of up to 88 unique participants (16 in Part 1, up to 30-40 initially in Part 2 [and potential expansion to 50-60 post formal IA and protocol amendment], and a maximum of 12 in Part 3) are planned to be randomized in this study.

In Part 1, for individual participants, the total duration of participation from the Screening visit to the telephone Follow-up visit will be 9 weeks (minimum) to 14 weeks (maximum) - as summarized in Figure 1.

In Part 2, the total duration of participation in the study, for ***each*** participant, will be 8 weeks (minimum) to 12 weeks (maximum), including the interval from the 1st Screening visit to the telephone Follow-up visit – refer to Figure 2.

In Part 3, if conducted, the total duration of participation for each participant, from the Screening to the telephone Follow-up visit, will be 5 weeks (minimum) to 10 weeks (maximum) – as outlined in Figure 3.

4.2. Scientific Rationale for Study Design

4.2.1. Study Population

As is typical in the case for FIH studies, the population planned for this study will be ***healthy***, adult males and females. However, studies to evaluate the development toxicity of PF-07202954 have ***not*** been conducted and hence, the use of a highly effective method of contraception is required in males and females of childbearing potential (refer to Section 10.4).

In Part 1 and Part 3 (if conducted), the healthy population will be limited to the typical upper age limit (to 55 years) and BMI limits (to ≤30.5 kg/m^2). However, in Part 2, allowance will be made to expand the age (to 65 years) and BMI limits (to ≤35.4 kg/m^2) to enable ability to screen participants with simple hepatic steatosis, a benign condition notable for accumulation of liver fat of ≥5%, and thereby assess the effect of PF-07202954 on liver fat CCI [redacted] following 14 days of inpatient dosing. Ability to detect reductions in liver fat CCI [redacted] with this duration of dosing with orally administered other DGAT2i is precedented.[11,12] In addition, ***the population dosed in Part 2*** will be confirmed as meeting ***all*** of the following criteria via ***double-confirmation*** between Screen ***and*** Day -2 visits:

- Liver fat as assessed via quantitative ultrasound parameter CAP™ of ≥270 dB/m, assessed using FibroScan® CCI [redacted]
- Liver stiffness as assessed via quantitative ultrasound parameter VCTE™ of <7.0 kPa, assessed using FibroScan® (suggestive of lack of inflammation/fibrosis as a result of abnormally accumulated liver fat);[10]
- ALT *and* AST ≤1.5 x ULN.

While this study includes 3 Parts, a given participant can only be randomized and dosed in 1 of the 3 parts; participants are ***not*** permitted to be randomized and dosed in multiple parts of this study. This restriction is placed to permit clinical experience with PF-07202954 to be garnered in *unique* participants.

4.2.2. Rationale for Part 1

Given the current study is the first time PF-07202954 will be administered to humans, an escalating single oral dose design is planned with careful assessment and ongoing review of safety data and PK of PF-07202954. Part 1 is designed as a randomized, dose -escalating, cross-over, interleaving, placebo-controlled, 2-cohort, study with dosing of study intervention (PF-07202954/placebo) planned following ≥10 hours overnight fast, at approximately 8:00AM (±2 hours) to occur ***with*** standard morning meal provided ~30 mins

prior to dosing at 0H. By design, at each dose level, 6 participants are planned to receive PF-07202954 and 2 participants are planned to receive placebo with all participants at the end of Part 1 having received 1 dose of placebo and up to 3 ***unique*** doses of PF-07202954. The rationale for selection of the starting (ie, first) dose level in Part 1 is outlined in Section 4.3.3. In addition, the highest anticipated steady-state AUC_{24} and C_{max} for PF-07202954 in Part 1 will ***not*** exceed the pre-identified stopping exposure limit determined based on nonclinical toxicity study (refer to Section 6.6.1) ***nor*** exceed the highest feasible total daily dose of 2000 mg.

The design of Part 1 permits both a within and between participant assessment of safety/tolerability and dose-response for PK and exploration of effect on plasma PCSK9. Furthermore, to permit an unbiased assessment of safety, the administration of active versus placebo in each Period will be double-blinded to both site staff (except those involved in preparation of doses) as well as the participants. However, to permit real-time review of the safety and PK data, the sponsor will be unblinded, although measures to limit degree of unblinding will be exercised – refer to Section 9.5 for details. In light of the findings in the 6 week toxicity studies in rats and monkeys, the safety assessments envisioned in this study administrating investigational product for the first time to humans are outlined in Section 8.2.

For a given participant, dosing will be separated by ≥**10 days**, with this planned dosing interval deemed sufficient based on the predicted PF-07202954 effective half-life of approximately 8 hours. In addition, this interval accounts for the required time for review of the safety, tolerability, and PK data from each dosing period before making a decision on the subsequent PF-07202954 dose to be evaluated. The planned doses in the escalation sequence (refer to Table 3) may be modified or repeated, as guided by emerging safety and PK data but will follow the dose-escalation rules defined in Section 6.6.1. The data from participants as they receive placebo will be pooled and compared to data from each active dose to determine the next escalating dose of PF-07202954. The assessment of the full range of doses will require the planned 8 Periods of dosing (4 Periods per participant). In the event that additional dose-escalation is no longer warranted (eg, maximum tolerated dose identified, clear evidence of plateau in plasma PK based on observed data with at least 2 dose-levels), the additional periods in this 4-Period, cross-over design may be used to repeat a previously administered dose, study a lower and/or intermediate dose, and/or undertake an exploratory assessment of plasma PK with dosing following an overnight fast of ≥10 hours ***or*** dosing following a high fat/high caloric morning meal (compared to dosing following a standard morning meal in previous Periods within the same cohort) to explore any potential food effect. And pending observed plasma PK data from Part 1, this study may also conduct Part 3 – refer to Section 4.2.4 – to compare plasma PK following dosing in the fasted state (Reference) to dosing with a high-fat/high-caloric morning meal (Test).

4.2.3. Rationale for Part 2

The initiation of Part 1 and Part 2 of this study will be staged. The first dose level in Part 2 will only initiate ***after*** at least 3 dose-levels, in Part 1, have been administered and safety plus PK data reviewed – refer to Section 4.3.4 for additional details regarding determination of the initial dose in Part 2 relative to dose(s) evaluated in Part 1. In addition, the highest anticipated steady-state AUC_{24} and C_{max} for PF-07202954 in Part 2 will *not* exceed the highest single oral dose exposure observed to have an acceptable safety profile in Part 1 of this study ***nor*** exceed the highest feasible total daily dose of 2000 mg.

Part 2 of this study is designed to assess the safety, tolerability, and PK, as well as potentially assess/explore markers of clinical activity of escalating doses of PF-07202954 administered once daily for 14 days. In each cohort/dose level, 8 of the 10 participants randomized will receive PF-07202954 and 2 will receive placebo. At the end of the study, the intent will be to pool the participants who received placebo across the cohorts in Part 2 into 1 group.

The proposed duration of dosing (14 days) is deemed to be sufficient to assess steady-state safety, tolerability, PK, as well as explore effect on PF-07202954 on markers of clinical activity, given the projected plasma half-life of approximately 8 hours and afforded by the completed, GLP, 6 week, toxicity studies in rats and monkeys. The planned doses in the escalation sequence (refer to Table 4) may be modified or repeated, as guided by emerging safety, tolerability, and PK data (as well as data assessing clinical activity, when available). In all cases, doses selected will follow the dose-escalation rules defined in Section 6.6.1.

To permit an unbiased assessment of safety, the administration of active versus placebo will be double-blinded to site staff (except those involved in preparation of doses) and the participants. However, to permit real-time review of the safety and PK data (as well as data assessing clinical activity), the sponsor will be unblinded, although measures to limit degree of unblinding will be exercised — refer to Section 9.5 for details. In light of the findings in the 6 week toxicity studies in rats and monkeys, the safety assessments are envisioned to be the standard used by the sponsor in trials administrating investigational product for the first time to humans as outlined in Section 8.2.

Based on nonclinical data, the potential exists that PF-07202954 causes induction of CYP3A4 mRNA. CCI [redacted]

In vitro data indicate that PF-07202954 is an inhibitor of the renal transporter MATE1 at clinically relevant concentrations. MATE transporters are involved in tubular secretion of organic cations in the kidney.[13] CCI [redacted] Creatinine is actively secreted by OCT2/MATE in the kidney. In the setting of OCT2/MATE inhibition, SCr levels have been

reported to increase slightly.[13] In order to assess the possibility of OCT2/MATE inhibition-related increases in SCr, SCysC will be collected in the standard safety labs, in addition to creatinine, in order to evaluate eGFR[15] – refer to Section 7.1.2 for additional details.

4.2.3.1. Assessment of Clinical Activity in Part 2

CCI [redacted]

The effect of PF-07202954 on the primary pharmacology CCI [redacted] will be measured and potential dose-response characterized for this effect CCI [redacted] – refer to Section 9.4.4.1. Using this design, the cumulative number of participants dosed with placebo (n=8) along with the 8 participants at each dose of PF-07202954 would allow for potential characterization of the dose response for the effect of PF-07202954 CCI [redacted].

4.2.4. Rationale for Part 3

Conduct of Part 3 in this study is conditional on whether exploration of plasma PK using fasted (and/or high-fat/high-caloric meal) was undertaken in Period 4 in 1 or both cohorts in Part 1 ***or*** if the results of the exploratory food effect in Part 1 is inconclusive (eg, due to large variability in plasma PK).

Pending observed data in Part 1 (including *potential* assessment of plasma PK with dosing following an overnight fast of ≥10 hours – refer to Section 4.2.2) and Part 2, where dosing will occur with a standard morning meal, assessment of the effect of a high-fat/high-caloric meal versus a fasted state on the PK of PF-07202954 may be conducted in Part 3. **If** Part 3 is conducted, it will occur only ***after*** completion of Part 1, though it *may* occur in parallel to Part 2. Part 3 will be conducted at the discretion of the sponsor.

This part will be a single cohort, randomized, open-label, 2-period, crossover design, randomizing 8 (minimum) to 12 (maximum) participants who will receive PF-07202954 once with a high-fat/high-caloric meal and once following an overnight fast of ≥10 hours with the order randomly assigned. Since the dose in this part (refer to Section 4.3.5) will be selected based on observed safety, tolerability, and PK of single doses in Part 1 *and* the dose selected will be lower than the highest dose tested in Part 1, standard safety monitoring will be used in this part of the study.

4.2.5. Rationale for Dosing with Standard Meal in Part 1 and Part 2

In Part 1 and Part 2 of this study, PF-07202954 will be administered with a standard morning meal because PF-07202954 is expected to be administered with food in clinical practice and administration with a meal helps in the assessment of the effect of PF-07202954 CCI [redacted] Although food is expected to have minimal impact on PF-07202954 exposures at doses ≤1500 mg based on the physical and chemical properties of PF-07202954 and simulations of a PBPK model, the effect of a high-fat/high-caloric meal on plasma concentrations of PF-07202954 may be evaluated in Part 1 and/or Part 3 of this study.

CCI [redacted]

4.2.7. Rationale for Banked Sample Collection

Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention – refer to Section 8.7.2.

4.3. Justification for Dose

The proposed doses of PF-07202954 in Part 1 (single, escalating doses) and Part 2 (repeated, escalating doses) were derived based on cumulative nonclinical data including in vitro and in vivo pharmacology and PK data and the 6-week toxicity studies completed in rats and monkeys. The PF-07202954 doses in Part 1 and Part 2 beyond the starting dose in Part 1 may be modified based on emerging human safety, tolerability, and PK data in the current study.

4.3.1. Projected Human PK Parameters and Effective Human Dose

In humans, PF-07202954 is predicted to have a CL_{plasma} of 3.34 mL/min/kg (hepatic clearance of 1.34 mL/min/kg; renal clearance of 2.0 mL/min/kg), F of 32% (oral absorption of 35%), V_{ss} of 2.30 L/kg, and an effective $t_{½}$ of approximately 8 hours.

The average total C_{eff} for PF-07202954 over the once daily dosing interval of 76.6 ng/mL (66.8 nM unbound), is equivalent to approximately IC_{85} of the in vitro human biochemical and human hepatocyte potencies. This exposure is projected with a clinical dose of 80 mg administered once daily of PF-07202954 and predicted to lower hepatic steatosis by ≥35% following 14 days of dosing (ie, similar magnitude as observed following 14 days of

dosing of 2 other oral DGAT2i).[11,12] At the PF-07202954 dose of 80 mg administered once daily, projected exposures are total C_{max} of 106 ng/mL and total AUC_{24} of 1840 ng•h/mL.

4.3.2. Human Exposure Limits

Guided by the target organs of toxicity identified in the completed GLP, 6 week studies in rats and monkeys (refer to Section 2.2.4, Table 3 and Table 4), the PK exposure limits in this study are proposed as –

- **In Part 1 and Part 2: Total C_{max}: 1450 ng/mL** – reflecting the *conservative* $1/10^{th}$ of the exposure at the NOAEL dose (100 mg/kg/day) in the 6 week toxicity study in monkeys [for the convulsions observed in 1 monkey in the exploratory toxicity study following PF-07202954 dose of 500 mg/kg/day];

- **In Part 1: Total AUC_{24}: 18,400 ng•h/mL** – reflecting 50% of exposure in males at the NOAEL dose (300 mg/kg/day) in the 6-week toxicity study in rats [for adverse renal findings];

- **In Part 2: Total AUC_{24}: 3,680 ng•h/mL** – reflecting 10% of exposure in males at the NOAEL dose (300 mg/kg/day) in the 6-week toxicity study in rats [for adverse renal findings] with revision to this stopping limit to be considered, via a protocol amendment post formal interim analysis, based on observed data in Part 1 *and* Part 2 in this study.

4.3.3. Rationale for Dose Selection in Part 1

The objective of Part 1 of this study is to explore the safety, tolerability, and plasma PK of PF-07202954 after administration of single escalating oral doses across a wide exposure range and potentially up to the maximum predefined human exposure limits (Table 3). Dosing will occur with a ***standard*** morning meal. The doses presented are projected based on nonclinical data and may be modified based on emerging human safety, tolerability, and PK data. Human PK parameter estimates, toxicokinetic data, and projected effective concentrations were used to establish the initial range of planned doses in this study. The projected human exposures are based on assuming dose-proportional increases in exposure within the planned dose range.

Table 3. Predicted Human Exposures at Proposed *Single* Doses of PF-07202954

Dose (mg)	*Total* Concentrations		Safety Margins[b,c]	
	C_{max}[a] (ng/mL)	AUC_{24}[a] (ng•h/mL)	C_{max}[b]	AUC_{24}[c]
10	10	180	140	102
30	31	540	46	34
100	100	1800	14	10
300	310	5400	4.6	3.4
600	620	11,000	2.3	1.7
1000[d]	1040	18,000	1.4	1.0[d]

a. C_{max} and AUC_{24} were estimated using projected human PK parameters for PF-07202954 *using* CL_{plasma}=3.34 mL/min/kg; V_{ss}=2.3 L/kg; F=0.32; ka=0.2 h^{-1}; human fu=0.382; body weight=70 kg.
b. C_{max} safety margins at the proposed doses were calculated based on total exposure at 1/10th of the exposure at the NOAEL dose in the 6 week toxicity study in monkeys [for the convulsions in 1 monkey in the exploratory toxicity study following PF-07202954 dose of 500 mg/kg/day]; human PF-07202954 C_{max} exposures will be limited to total C_{max}=1450 ng/mL.
c. AUC_{24} safety margins at the proposed doses were calculated based on 50% of total exposure at the NOAEL dose in the 6-week toxicity study in rats [for adverse renal findings]; human PF-07202954 AUC_{24} exposures will be limited to total AUC_{24}=18,400 ng•h/mL.
d. Highest feasible total daily dose is 2000 mg; dose-increments as well as maximum dose may be adjusted up or down as guided by observed safety/tolerability, and plasma PK but projected PK will ***not*** exceed PK stopping limits.

The starting dose of PF-07202954 was informed by the on-target effect of DGAT2i – namely, in vitro human DGAT2 biochemical and hepatocyte assays as well as results from the evaluation of 2 oral DGAT2i[11,12] for effect on hepatic steatosis following 14 days of dosing. The 10 mg starting dose of PF-07202954 was selected as it is projected to achieve approximately IC_{50} for DGAT2 inhibition at C_{max} with this exposure, when adjusted for potency differences which were found to be well tolerated with 2 other DGAT2i.[11,12] Furthermore, adverse effects due to off-target effects are not expected at this low starting dose based on completed toxicity studies with PF-07202954 in rats and monkeys.

The dose range to be studied was selected to bracket the expected clinically effective dose range in humans for clinically relevant pharmacological activity of hepatic steatosis and providing safety coverage for a wide range of PF-07202954 doses.

The dose/exposure- escalation increments are planned to be up to approximately semi-logarithmic increases ***in exposure*** from the previous highest dose. The actual doses, target exposures, and/or dose 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 and the dose-escalation, and stopping rules outlined in Section 6.6.1.

4.3.4. Rationale for Dose Selection in Part 2

The objective of Part 2 of this study is to assess the safety, tolerability, and PK along with explore effect on markers of clinical activity with administration of repeated, escalating doses of PF-07202954 across a wide exposure range. The dosing frequency will be once daily for 14 days with dosing occurring with a ***standard*** morning meal.

In Part 2, the selection of the starting dose will be: **(1)** at least ≤ semi-logarithmic lower than a dose previously administered in Part 1 and observed to have an acceptable safety profile; **(2)** projected to have total daily steady-state exposures (C_{max}, C_{min}, and AUC_{24}) that have been observed to be well-tolerated following single dose administration in Part 1; and **(3)** accounting for the accumulating safety and tolerability data from the escalating doses in Part 1 with the understanding that dosing in Part 2 may be paused or stopped based on emerging safety signals.

The proposed starting dose level, in Part 2, is 10 mg once daily with this dose projected to elicit minimal clinical activity with anticipated C_{max} more than 5-fold lower than C_{eff}. The proposed doses, along with anticipated margins over the PK stopping limits are summarized in Table 4.

Table 4. Predicted Human Steady-State Exposures at Proposed *Repeated* Doses of PF-07202954

Dose (mg/day)	*Total* Concentrations		Safety Margin[b,c]	
	C_{max}[a] (ng/mL)	AUC_{24}[a] (ng•h/mL)	C_{max}[b]	AUC_{24}[c]
10	13	230	110	16
30	39	680	37	5.4
100	130	2300	11	1.6
160	210	3600	6.9	1.0
300[d]	390	6800	3.7	0.54[d]
600[d]	790	14,000	1.8	0.26[d]
1000[d]	1300	23,000	1.1	0.16[d]

a. C_{max} and AUC_{24} were estimated using projected human PK parameters for PF-07202954 *using* CL_{plasma}=3.34 mL/min/kg; V_{ss}=2.3 L/kg; F=0.32; ka=0.2 h^{-1}; human fu=0.382; body weight=70 kg.

b. C_{max} safety margins at the proposed doses were calculated based on total exposure at 1/10th of the exposure at the NOAEL dose in the 6 week toxicity study in monkeys [for the convulsions in 1 monkey in the exploratory toxicity study following PF-07202954 dose of 500 mg/kg/day]; human PF-07202954 C_{max} exposures will be limited to total C_{max}=1450 ng/mL.

c. AUC_{24} safety margins at the proposed doses were calculated based on 10% of total exposure at the NOAEL dose in the 6-week toxicity study in rats [for adverse renal findings]; human PF-07202954 AUC_{24} exposures will be limited to total AUC_{24}=3,680 ng•h/mL – with revision to this stopping limit to be considered, via a protocol amendment post formal interim analysis, based on observed data in Part 1 *and* Part 2 in this study.

d. Highest feasible total daily dose is 2000 mg; dose-increments as well as maximum dose may be adjusted up or down as guided by observed safety/tolerability, and plasma PK (as well as data reflecting clinical activity) but projected PK will ***not*** exceed PK stopping limits; furthermore, these higher dose(s) may be evaluated based on observed data in Part 1 *and* Part 2 in this study but only after a protocol amendment.

The starting dose may be refined to be as low as 5 mg, and as high as 20 mg, once daily, guided by observed safety/tolerability and plasma PK in Part 1. As planned, the starting dose in Part 2 will not exceed 20 mg once daily. Subsequent cohorts will receive escalating doses, at approximate semi-logarithmic increments ***in dose/exposure,*** as guided by observed safety/tolerability, and plasma PK with repeated dosing. ***In addition***, emerging data reflecting markers of clinical activity CCI [redacted] will be considered in determination of maximum repeated dose-level of PF-07202954 evaluated. In all cases, the projected exposure at the highest dose evaluated will *not* exceed the preidentified PK stopping limits.

The range of doses proposed in Part 2 are also motivated by the objective to characterize the dose-response for effect of PF-07202954 in liver fat CCI As such, across the proposed dose levels, it is envisioned that at least 1 dose will be at or below, plus additional doses above, the projected ED_{50} for effect on liver fat.

4.3.5. Rationale for Dose Selection in Part 3

As outlined in Section 4.2.4, conduct of Part 3 is conditional on results from Part 1. If Part 3 is conducted, a single dose level of PF-07202954 will be evaluated. Dose selection will be based on emerging safety, tolerability, and PK data from Part 1 and Part 2, in this study. The dose for Part 3 will be less than or equal to the highest dose tested in Part 1 observed to be well tolerated. CCI

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed ***all phases for a given Part*** (ie, 1, 2, or 3) of the study, including the last scheduled procedure shown in the SoA-Table A, SoA-Table B, and SoA-Table D.

The end of the study is defined as the date of the last visit of the last participant in the study, globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. ***In Part 1 and Part 3***, male and female participants must be 18 to 55 years of age, inclusive, at the time of signing the ICD:

    - ***In Part 2,*** the upper limit of acceptable age will be extended to 65 years, inclusive, at the time of signing the ICD;

- Refer to Section 10.4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Male and female participants who are ***healthy*** as determined by medical evaluation including medical history, PE, laboratory tests; *plus* **in Part 1 only**, cardiac telemetry monitoring.

3. ***In Part 2, only***, at Screen ***and*** Day -2, meet the following criteria based on assessment via FibroScan®, with a single repeat permitted, ***on a separate day***, to assess eligibility, if needed, at ***each*** of these 2 visits:

   - CAP™ ≥270 dB/m;

   - VCTE™ <7.0 kPa.

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

Weight:

5. BMI of ≥17.5 ***and*** ≤ 30.5 kg/m^2 and a total body weight >50 kg (110 lb):

   - ***In Part 2,*** upper limit of acceptable BMI will be extended up to 35.4 kg/m^2, inclusive;

   - ***In all 3 Parts***, a single repeat assessment of body weight and/or BMI permitted *on a different day* to assess eligibility, if needed.

Informed Consent:

6. Capable of giving signed informed consent as described in Section 10.1, 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, CV, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

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

3. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb, or HCVAb; *though* hepatitis B vaccination (*or* HBsAb positive result) is allowed.

4. Other 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:

5. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 -half-lives (whichever is longer) prior to the first dose of study intervention - refer to Section 6.5 for additional details.

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

7. Results as reported by the sponsor-identified laboratory(ies), ***at Screen in all 3 Parts (and Day -2, in Part 2)*** as below with a single repeat of ***any*** of these parameters permitted to assess eligibility, if needed:

    - ALT >ULN (in Part 1 and Part 3) ***or*** >1.5x ULN (in Part 2, only);
    - AST >ULN (in Part 1 and Part 3) ***or*** >1.5x ULN (in Part 2, only);
    - ALP >2x ULN;
    - TBili >ULN ***and*** direct bilirubin >ULN:
        - **Note:** Participants with a history of Gilbert syndrome would be eligible for this study provided direct bilirubin level is ≤ ULN, and hemoglobin and reticulocyte count are within the reference range of the sponsor-identified laboratory(ies).
    - Fasting Plasma Glucose >125 mg/dL (6.9 mmol/L);

- Fasting serum TG >150 mg/dL (1.69 mmol/L) – in **Part 1 and Part 2:**
  - Part 3 does *not* include assessment of markers of clinical activity CCI [redacted] hence no associated exclusionary criteria proposed.
- eGFR (using serum creatinine and CKD-EPI formulae) of ≤90 mL/min/1.73 m^2 at time of signing ICD;
- UACR >30 mg/g on spot urine collection;
- UPCR >200 mg/g on spot urine collection.

8. A positive urine drug test for illicit drugs as reported by laboratory, ***at Screen in all 3 Parts (and Day -2, in Part 2, only)***; this single laboratory assessment is ***not*** permitted to be repeated to confirm eligibility.

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

10. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results:
    - *Examples include* - baseline QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias;
    - If the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting –
      - If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility;
      - Computer-interpreted ECGs should be overread by a physician/medical provider experienced in reading ECGs before excluding participants.

Other Exclusions:

11. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening:

    - Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours;

    - As a general rule, alcohol intake should not exceed 14 units per week (in males) and 7 units per week (in females) – where 1 unit = 8 oz. (240 mL) beer, 1 oz. (30 mL) of 40% spirit, or 3 oz. (90 mL) of wine.

12. Use of tobacco- or nicotine- containing products ***in excess*** of the equivalent of 5 cigarettes per day or 2 chews of tobacco per day.

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

14. History of sensitivity to heparin or heparin-induced thrombocytopenia ***only if*** heparin is used to flush IV catheters used during serial blood collections.

15. Unwilling or unable to comply with the lifestyle considerations outlined in Section 5.3.

16. ***In Part 2 only,*** participants meeting criteria for contraindication to undergoing imaging assessments including –

    - Active placement of medical devices in/on thoracic cavity as these interfere with use of ultrasound-based imaging modalities, and MRI;

    - History/evidence of ***any*** of the following:

        - Contraindication to MRI such as ferric implant;

        - History of severe claustrophobia impacting ability to perform MRI during the study even despite mild sedation/treatment with a ***short-acting*** anxiolytic;

        - Inability to lie still within the *closed* environment of the MRI scanner *or* maintain a breath hold for the required period to acquire images *even despite* mild sedation/treatment with an anxiolytic.

17. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

Randomization Criteria – Parts 1, 2, and 3

Participants will be randomized into the study provided they have satisfied **all** the following criteria:

- Eligibility criteria outlined in Section 5.1 and Section 5.2;
- *In addition*, prior to dosing on Day 1, the results of the clinical laboratory tests (including urine drug test) ***conducted upon each inpatient admission*** must be deemed to have no clinically significant findings, in the opinion of the PI, and as such permit (continued) participation in this study.

In Part 1, participants in the 2 cohorts will be randomized per the scheme summarized in Table 5 with the actual dose administered following the proposed dose-escalation approach outlined in Section 4.3.3 and Table 3.

Table 5. Study C4171001 - Part 1 - Randomization Scheme

Cohort	Sequence	Period[a]			
		1	2	3	4[b]
1 (n=8)	1 (n=2)	Placebo	Dose 3	Dose 5	Dose 7[c]
	2 (n=2)	Dose 1	Placebo	Dose 5	Dose 7[c]
	3 (n=2)	Dose 1	Dose 3	Placebo	Dose 7[c]
	4 (n=2)	Dose 1	Dose 3	Dose 5	Placebo[c]
2 (n=8)	5 (n=2)	Placebo	Dose 4	Dose 6	Dose 8[c]
	6 (n=2)	Dose 2	Placebo	Dose 6	Dose 8[c]
	7 (n=2)	Dose 2	Dose 4	Placebo	Dose 8[c]
	8 (n=2)	Dose 2	Dose 4	Dose 6	Placebo[c]

a. In each dose level/Period, the dose being evaluated will be known to the investigator(s) and participants; however, to preserve the double-blind design which participant is receiving PF-07202954 versus placebo will not be known by the investigator(s) and participants.
b. Pending observed safety/tolerability and plasma PK in previous Periods, an exploratory assessment of plasma PK with dosing following an overnight fast of ≥10 hours and/or dosing with high-fat/high-caloric meal (compared to dosing following a standard morning meal in previous Periods) may be considered.
c. Dose 7 and/or Dose 8 if used to assess plasma PK with dosing in fasted state and/or post high-fat/high-caloric meal – pending observed safety, and PK in previous Periods – will limit the within-participant assessment of food effect to 4 participants on PF-07202954.

In Part 2, participants in each cohort will be randomized to PF-07202954 or placebo in a 4:1 ratio with 10 participants dosed in each cohort.

In Part 3, **if conducted**, a total of 8 (minimum) to 12 (maximum) participants will be randomized to receive PF-07202954 in the 2 periods – once with a high-fat/high-caloric meal and once following an overnight fast of ≥10 hours – with the order randomly assigned.

5.3. Lifestyle Considerations

After confirmation of eligibility at Screen, participants will be instructed to maintain the following guidelines starting prior to ***each*** inpatient admission *and* for the duration of their participation in the study.

5.3.1. Meals and Dietary Restrictions

While inpatient, the meals consumed are expected to follow the restrictions outlined below with participants encouraged to complete each meal.

- Participants must abstain from all food and drink (except water) –
  - ***At least 4 hours*** prior to any non-lipid-related safety laboratory evaluations;
  - ***At least 10 hours*** prior to fasting clinical laboratory evaluations when fasting lipid panel is included.
- 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.
- Water may be consumed *without restrictions* both prior to *and* after study intervention administration when dosing occurs following a standard morning meal (***or*** high-fat/high-caloric meal).
- **Meals in Part 1 and Part 2:**
  - All meals are standard meals ***unless*** Period 4 in 1 or both cohorts ***in Part 1*** are used to explore effect of fasted state and/or high-fat/high-caloric meal on plasma PK.
  - 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 dosing days:
    - ***In Part 2,*** on days of CCI assessment, time of meal(s) ***may*** be adjusted to aide scheduling this assessment at the CCI facility ***while maintaining*** the minimum required pre-procedure fast of ≥4 hours.
  - The total daily nutritional composition should be **approximately 55% carbohydrate, 30% fat, and 15% protein:**
    - The daily caloric intake per participant should not exceed approximately 3200 kcal;
    - If participants cannot complete the meals, the portion consumed in 25% increments will be documented and potential impact on results assessed by the sponsor study team on a case-by-case basis.

- On *dosing days* while inpatient:
  - Standard morning meal will be provided following on overnight fast of ≥10 hours ***and*** at approximately 30 minutes prior to dosing at 0 H (**or** similar clock time on non-dosing days), consumed over approximately a 20-minute period (ie, completed approximately 10 minutes prior to dosing);
  - Lunch will be provided approximately 5 hours after morning dosing, at 0H;
  - Evening meal will be provided approximately 12 hours after morning dosing, at 0H;
  - An evening snack may be permitted; however, the need to ensure an overnight fast of ≥10 hours is required to enable assessment of clinical laboratory tests the next morning.
- ***In Part 1, Period 4 only***, dosing may be altered (refer to Section 4.2.2) and can occur either following an overnight fast of ≥10 hours and/or with a high-fat/high-caloric meal; if this occurs, dosing will occur per the conditions outlined below for Part 3.

- **Meals in Part 3 (if conducted) will be standard *or* high-fat/high-caloric breakfast:**
  - **In both Periods** while inpatient, as appropriate, standard breakfast (*except* Day 1), lunch, and evening meals (along with an evening snack) are to be provided at a similar clock time to when these meals are offered on dosing days;
  - The total daily nutritional composition should be approximately **55% carbohydrate, 30% fat, and 15% protein –** in ***both*** Periods;
  - ***Dosing in Fasted State*****: On Day 1**, dosing will occur following an overnight fast of ≥10 hours with water **only**, with the standard morning meal **not** offered:
    - ***When dosing is in the fasted state***, water is permitted until 1 hour prior to dosing and water may be consumed without restriction beginning at 1 hour after dosing.
  - ***Dosing in Fed State*****: On Day 1**, following an overnight fast of ≥10 hours, participants should start a **high-fat/high-caloric breakfast** approximately 30 minutes prior to PF-07202954 administration:
    - This breakfast will be consumed over approximately *20-minute interval* and PF-07202954 administered within approximately 10 minutes after completion of the meal at 0H;

- Breakfast will be a high-fat/high-caloric meal consistent with the FDA recommendation for a high-fat/high-caloric meal with a representative example being: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz. of hash brown potatoes, and 8 oz. of whole milk.

- Lunch will be provided approximately 5 hours after morning dosing at 0H;

- Evening meal will be provided approximately 12 hours after morning dosing;

- An evening snack may be permitted; however, the need to ensure an overnight fast of ≥4 hours is required to enable assessment of clinical laboratory tests the next morning.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for **≥24 hours** prior to the start of dosing until collection of the final PK sample in *each* study period (in Part 1 and Part 3) ***or*** last PK collection prior to discharge from the CRU (in Part 2);

- 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.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for **≥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***;

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

- Participants will be advised to avoid direct sunlight exposure or any high intensity UV light exposure, from the first day of dosing with study intervention and until the on-site Follow-up visit. In addition, participants will be instructed to wear eye protection and apply sun cream/lotion with a high sun protection factor, as appropriate.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At timepoints indicated in the schedule of activities (SoA-Table A, SoA-Table B, and SoA-Table D), 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). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are ***not*** subsequently randomly assigned to study intervention/enrolled in the study. Screen failure data are collected and remain as source and are ***not*** reported to the clinical database.

Individuals who do ***not*** meet the criteria for participation in 1 of the 3 Parts of this study ***and*** are screen failed may be rescreened for a ***different*** Part of this 3-Part study.

6. STUDY INTERVENTION

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

For the purposes of this protocol, the term investigational product (ie, IP) may be used synonymously with study intervention and refers to all of the following:

- Placebo for PF-07202954;
- PF-07202954.

6.1. Study Intervention(s) Administered

For all parts of this study, PF-07202954 and placebo will be provided by Pfizer as bulk powders for extemporaneous preparation of oral suspension at the CRU.

PF-07202954 and placebo will be presented to the participants in individual dosing containers.

6.1.1. Administration

- ***Part 1 and Part 2:*** following an overnight fast of ≥10 hours, participants will receive the study intervention with a standard morning meal at approximately 08:00 hours (±2 hours):

  - *NOTE:* if ***up to 2*** of the 8 periods in Part 1 are being utilized to assess plasma PK in the fasted state and/or with high-fat/high-caloric meal, dosing will occur in the appropriate/respective setting (ie, overnight fast of ≥10 hours or with high-fat/high-caloric meal).

- ***Part 3:*** following an overnight fast of ≥10 hours, participants will receive the study intervention either with water (fasted state) ***or*** with a high-fat/high-caloric meal at approximately 08:00 hours (±2 hours), in each of the 2 Periods, per randomization assignment.

In all cases, investigator site personnel will administer study intervention during each period with ambient temperature water to a total volume of approximately 240 mL;

- Adequate measures to ensure taste masking will be performed ***prior to*** administration of the study intervention, if needed;

- Additional water (up to 120 mL) *may* be consumed by the participants (eg, extra rinse) in an attempt to ensure that the full dose is consumed – with such instances documented in the source at the site;

- Administration of study intervention will occur according to the EDR;

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

6.2. Preparation/Handling/Storage/Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a

minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

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

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

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

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

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

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

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

6.2.1. Preparation and Dispensing

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

For Parts 1, 2, and 3: PF-07202954 and placebo oral dosing suspensions will be prepared in the CRU by 2 operators, 1 of whom is a pharmacist. Details of dose preparation will be given in a separate EDR. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

For Parts 1 and 2: In order to maintain the blind, PF-07202954 and placebo will be prepared by qualified unblinded site personnel according to the EDR with study intervention administered in a blinded fashion to the participant.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation 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.

Participants will be randomly assigned to receive study intervention from a central randomization scheme. ***In Part 1 and Part 2***, 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 (for example, a pharmacist) will be responsible for the preparation and dispensing of all study intervention according to the randomization schedule and assigned treatment for the individual participant.

For Part 3, the investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

6.3.2. Breaking the Blind – Part 1 and Part 2, only

The method for breaking the blind 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 sponsor 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 DCT.

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. A ***limited number*** of the sponsors' study team 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.

6.4. Study Intervention Compliance

In Part 1, Part 2, and Part 3, 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 DCT. 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.

6.5. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within **7 days** or **5 half-lives** (whichever is longer) prior to the first dose of study intervention –

- Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor;
- Acetaminophen/paracetamol may be used at doses of ≤1 gram per day;
- Females using estrogen containing hormonal contraceptives or taking estrogen containing HRT may be eligible to participate in this study ***if they are willing to discontinue therapy ≥28 days*** prior to the first dose of study intervention and remain off hormonal therapy for the duration of the study:
    - Depo-Provera® must be discontinued ***at least 6 months*** prior to the first dose of study intervention.

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

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

6.6. Dose Modification

The dosing schedule may be adjusted to repeat 1 or more dose level(s) to further evaluate safety, tolerability, or plasma PK of PF-07202954, and/or explore markers of clinical activity at a given dose level or to add cohorts to evaluate additional dose levels – as described in Section 4.3. The study procedures for these additional participant(s)/cohort(s) will be the same as that described for other study participants/cohorts in this protocol.

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 in Part 1 ***and*** separately in Part 2 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 defined as the following:

  - total C_{max}=1450 ng/mL (in Part 1 and Part 2);

  - total AUC_{24}=18,400 ng•h/mL (in Part 1);

  - total AUC_{24}=3,680 ng•h/mL (in Part 2 with revision to this stopping limit to be considered, via a protocol amendment post formal interim analysis, based on observed data in Part 1 ***and*** Part 2 in this study).

- 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 level will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data.

- ***Part 1:*** A minimum of 6 participants (including at least 1 participant who received placebo) of the planned 8 participants to be dosed at each dose level must complete dosing and planned assessment to a minimum of 24 hours post dose. Safety, tolerability, and plasma PK data through ***at least 24 hours post dose*** for the prior dose level (along with cumulative data from all previously administered doses) will be reviewed in order to identify the next dose-level to escalate to in the next period.

- ***Part 2:*** A minimum of 8 participants (including at least 1 participant who received placebo) of the planned 10 participants to be dosed at each dose level must complete the planned 14 days of dosing and planned safety/tolerability assessments to a ***minimum of 24 hours post dose on Day 14***.

  - In addition, plasma PK data through ***at least 24 hours post dose on Day 7*** (***or*** at least 24 hours post dose on Day 14 ***if*** the observed $t_{½}$ of PF-07202954 in Part 1 is greater than 30 hours) for the prior dose level (along with cumulative data from all previously administered doses) will be reviewed in order to identify the next dose-level to escalate to in the next period.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: AE, or some other (administrative) reason.

If study intervention is definitively discontinued, the participant will ***not*** remain in the study for further evaluation. See the SoA-Table A, SoA-Table B, and SoA-Table D for data to be collected at the time of discontinuation of study intervention.

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

7.1.1. ECG Changes

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

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

7.1.2. Potential Cases of Acute Kidney Injury

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

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level and increase of ≥30% in SCysC level relative to the participant's own baseline measurement should trigger another assessment of SCr and SCysC as soon as practically feasible, preferably ***within 48 hours from awareness***.

If the second SCr assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr increase relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), ***and*** if the second SCysC assessment (after the first observation of ≥30% increase relative to the participant's baseline measurement) remains increased by ≥30%, then further dosing of study intervention should be withheld. The participant should continue all safety assessments and adequate, immediate, diagnostic, and supportive measures taken to correct apparent acute kidney injury.

If a participant demonstrates concomitant SCr-based ***and*** SCysC-based eGFR decline of ≥30% compared to the participants' baseline concomitant SCr-based ***and*** SCysC-based eGFR, then the participant should not be further dosed and adequate, immediate, supportive measures including **urgent evaluation by a nephrologist (preferably within 24 hours) with appropriate management** and treatment as clinically indicated. Safety assessments should be repeated weekly or as indicated by the nephrologist until the renal parameters are deemed to be stable by the nephrologist and/or PI.

If the participant cannot be seen by a nephrologist within 24 hours (as described above), then the participant should be sent to a local emergency room for evaluation and treatment as clinically indicated.

Participants should return to the investigator site and be evaluated as soon as possible, ***preferably within 48 hours*** from awareness of the second assessment confirming abnormal eGFR result (ie, ≥30% decline in concomitant SCr-based ***and*** SCysC-based eGFR). This evaluation may include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr and SCysC, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, urinary indices, as well as UACR and UPCR. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury (ie, increase in SCr ***and*** increase in SCysC), with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr and/or SCysC. If ≥2 healthy participants in a ***given*** dose group (in each of the 3 Parts of the study, ***separately***) are noted to have 2 *consecutive* decreases from baseline in eGFR of ≥30%, based on concomitant SCr-based ***and*** SCysC-based eGFR, then an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.2. Participant Discontinuation/Withdrawal from the Study

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

- Refused further follow-up;
- 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 a given study site.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA-Table A, SoA-Table B, and SoA-Table D 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*** received at least 1 dose of the study intervention, and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

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

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow up

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

The following actions must be taken if a participant fails to 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the SoA-Table A, SoA-Table B, SoA-Table C, and SoA-Table D. Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in the SoA-Table A, SoA-Table B, SoA-Table C, and SoA-Table D 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 into 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, banked biospecimens, may be performed without repeat collection, as appropriate.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected ***prior*** to the insertion of the catheter. ***If*** an in-dwelling IV catheter is used for purposes of blood collection, **discard the first approximate 3 mL** of volume in the catheter prior to initiating collection of protocol-specified blood samples.

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 envisioned to be approximately **465 mL (Part 1), 540 mL (Part 2), and 205 mL (Part 3).** 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 60 consecutive days.

To prepare for study participation, participants will be instructed on the information outlined in Section 5.3 (related to Lifestyle Considerations) and Section 6.5 (regarding permitted/limited use of Concomitant Therapies) of this protocol.

8.1. Efficacy Assessments

No efficacy assessments are being undertaken in this study.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA-Table A, SoA-Table B, SoA-Table C, and SoA-Table D. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

During the on-going COVID-19 pandemic, as applicable, consistent with the investigator site(s) policy/SOPs, testing for SARS-CoV2 and safety monitoring of the participants will be implemented.

8.2.1. PEs

In this study, PEs are to be performed at nominal timepoints specified in the SoA-Table A, SoA-Table B, and SoA-Table D.

- 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 CV 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 ***body weight*** will also be measured and recorded as per the SoA-Table A, SoA-Table B, and SoA-Table D.

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;

- Assessment performed at approximately the same time of the day at each nominal timepoint, ***as much as practically possible***;

- And participants must also remove the contents of their pockets and remain still during measurement of weight.

8.2.2. Vital Signs

In this study, assessment of vital signs (including BP and pulse rate) will occur at the nominal timepoints specified in the SoA-Table A, SoA-Table B, SoA-Table C, and SoA-Table D per the following specifications:

- ***Single, supine BP and pulse rate*** will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after ≥***5 minute*** of rest;

- The same arm (preferably the dominant arm) will be used throughout the study;

- Participants should be instructed *not* to speak during measurements.

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

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

8.2.3. 12-lead ECGs

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

In Part 1, during conduct of the study: *Triplicate* 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected before dose administration on Day 1 of each period will serve as each participant's baseline QTcF value;

- However, ***for purposes of the CSR***, within-participant, time-matched assessment of each PF-07202954 dose relative to placebo, will be reported.

In Part 2, during conduct of the study and for purposes of reporting in the CSR: *Triplicate* 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected at 0H prior to dosing on Day 1 will serve as each participant's baseline QTcF value.

In Part 1 and Part 2, when triplicate, supine, 12-lead ECGs are collected, to ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any post dose QTcF interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 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.

In Part 3, during conduct of the study and for purposes of reporting in the CSR: *Single,* 12-lead ECGs obtained prior to dosing in *each* Period will serve as baseline for the given Period and to ensure safety of the participants, a qualified individual at the investigator site will make comparisons of post dose 12-lead ECGs to this baseline measurement. Additional ECG monitoring will occur if a) a post dose QTcF interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart 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 QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

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

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

ECG values of potential clinical concern are listed in Section 10.7.

8.2.3.1. Continuous Cardiac Monitoring by Telemetry – in Part 1, only

All abnormal rhythms will be recorded and reviewed by the study physician/medical provider for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the DCT. 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, as outlined in in SoA-Table A, 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, only.*** This may be done immediately prior to dosing or at some 2-hour continuous interval in the 24-hour interval 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.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical safety laboratory tests to be performed and the SoA-Table A, SoA-Table B, SoA-Table C, and SoA-Table D for the timing and frequency. All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA-Table A, SoA-Table B, SoA-Table C, and SoA-Table D. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within ***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 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.

Refer to Section 10.6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

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.

8.2.5. Pregnancy Testing

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

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

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

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator 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 definitively 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 AE or SAE after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor ***within 24 hours*** of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

8.3.3. Follow-up of AEs and SAEs

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

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

Further information on follow-up procedures is given in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until ***at least 28 days*** after the last dose of the 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 CT SAE Report Form is maintained in the investigator site file.

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

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

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

8.3.6. Cardiovascular and Death Events

N/A.

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

N/A.

8.3.8. Adverse Events of Special Interest

N/A.

However, the potential risks based on completed nonclinical toxicity studies are summarized in Table 1 may, based on ***observed data*** from this study, lead to 1 or more of these potential risks being classified as AESIs in the future.

8.3.8.1. Lack of Efficacy

N/A. Assessment of efficacy is *not* planned in the study population.

8.3.9. Medical Device Deficiencies

N/A.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of PF-07202954 greater than 4000 mg in a ***24-hour interval*** will be considered an overdose.

Sponsor does ***not*** recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07202954 (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis ***as soon as practically possible*** but at least within ***5 days*** from the date of the last dose of study intervention if requested by the 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 medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of PF-07202954 Concentrations – Parts 1, 2, and 3

Blood samples (**4 mL**), to provide sufficient plasma, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of PF-07202954 as specified in the SoA-Table A, SoA-Table B, SoA-Table C, and SoA-Table D.

- The actual times may change, but the number of samples will remain the same;
- All efforts will be made to obtain the samples at the exact nominal time relative to dosing – with the actual date and time (24-hour clock time) of each sample recorded;
- 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 DCT;

- 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 DCT;

- Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

Samples will be used to evaluate the PK of PF-07202954. Samples collected for analyses of PF-07202954 ***plasma*** concentrations may also be used to evaluate safety or clinical activity 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. These data will be used for internal exploratory purposes and will not be included in the CSR for this study.

Genetic analyses will ***not*** be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-07202954 will be analyzed using a validated analytical method in compliance with applicable SOPs.

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 timepoints 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.

8.5.2. Plasma for Qualitative Metabolite Profiling - Part 2, only

Blood samples (**4 mL** each) to provide sufficient plasma will be collected for metabolite screening into appropriately labeled tubes containing K_2EDTA at times specified in the SoA-Table C. These samples may be used for metabolite identification and/or evaluation of the bioanalytical method. 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. These data may be used for internal exploratory purposes and will ***not*** be included in the CSR for this study.

8.5.3. Urine for Analysis of PF-07202954 Concentrations – Part 2, only

Urine will be collected at times defined in the SoA-Table C.

Spot Urine Collection prior to dosing on Day 1, each participant will complete a forced void. Approximately **5 mL** aliquot from this urine ("urine blank") will be collected and stored frozen for measurement of PF-07202954 concentrations. This collection must occur prior to dosing on Day 1 but can be as early as first void on the morning and as late as 5 minutes prior to dosing.

For details regarding **24 hour urine collection** on Day 14, refer to Section 8.8.3.

All urine aliquots will be collected per detailed instructions offered in a laboratory manual. Urine samples will be analyzed using a validated analytical method in compliance with applicable SOPs.

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

Any deviation from the specified sample handling procedure resulting in compromised sample integrity, will be considered a protocol deviation.

As part of understanding the PK of the study drug, ***urine*** samples may also be used to evaluate safety or clinical activity 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. These data will be used for internal exploratory purposes and will not be included in the CSR for this study.

CCI [redacted]

CCI

[redacted]

Management of Incidental Findings

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study but is unrelated to the purpose and beyond the aims of the study.

The MRI images will be reviewed by the ***central review facility*** identified by the sponsor. The purpose of this review is to evaluate images for purposes of quantifying amount of liver fat and liver volume. Central image review is not a complete medical review of the participant. If, during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study sponsor for disclosure to the PI. All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician/-participant relationship. The PI will be responsible for reporting any AEs identified from incidental findings as described in the AE reporting section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

Assessment of Liver Fat and Liver Stiffness – using FibroScan® - in Part 2, only

In this study, assessments of liver fat and stiffness using FibroScan® will occur at scheduled visits outlined in the SoA-Table B. Each assessment will require the participants to be in a supine position for approximately 15 minutes with the image acquisition undertaken **following a fast (except water) of ≥4 hours**. The results for liver fat (via CAP™) in dB/m and liver stiffness (via VCTE™) in kPa will be displayed on the FibroScan® device at the end of each assessment and used to determine whether an individual participant qualifies to progress to dosing. Acquisition results do not need independent over-reading, but steps to ensure that acquisition was complete and accurate are required. Training is to be offered to **at least 2 site staff** (who *may* be sonographers or comparable) by **Echosens *and*** certified as operators based on this training by Echosens, at the start of the study. *As much as practically*

possible, attempts will be made to ensure each individual participants' assessment is performed by the same site staff throughout the study.

The summary of numerical results (including quality related outputs) must be printed and saved by the study site (or imaging facility, as applicable) as part of each participant's source documents. In addition, all images and output reports acquired must be saved by the study site until the conclusion of the study.

8.7. Genetics

8.7.1. Specified Genetics

A *single* **4 mL** blood sample (in K_2EDTA tube for DNA isolation) will be collected as outlined in SoA-Table A, SoA-Table C, and SoA-Table D. It will be analyzed to assess the impact of allelic variants of ABCG2 (encodes for BCRP), PNPLA3, and HSD17b13. Additionally, the sample may be used to evaluate other genetic variants for associations with variation in PK, clinical activity assessed as part of this study, or to explore AEs.

Genome-wide markers for controlling for ethnic-based genetic associations may also be assayed.

If needed (eg, in the event of DNA extraction failure), a replacement blood sample may be requested from the participant.

See Section 10.5 for information regarding genetic research.

8.7.2. Banked Biospecimens for Genetics

A **2 mL** blood sample optimized for DNA isolation (Prep D1.5) will be collected as local regulations and IRBs/ECs allow - as outlined in SoA-Table A, SoA-Table C, and SoA-Table D. ***If collection is missed*** at the designated time point, the sample may be collected at the next available timepoint when biospecimens are being collected.

Banked Biospecimens may be used for research related to the study intervention(s) and NAFLD/NASH. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

If needed (eg, in the event of DNA extraction failure), a replacement blood sample may be requested from the participant.

See Section 10.5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the study-specific laboratory manual offered to the site(s) ahead of study initiation.

CCI [redacted]

[redacted]

CCI

[redacted]

8.8.3. Interval Urine Collection

This sub-section covers details regarding ***interval*** urine collection for measurement of –

[redacted]

Over a **24-hour period, urine collection** will be undertaken at times specified in the SoA-Table A, and SoA-Table C –

- Each interval urine collection ***will start*** with a forced void which can be used for other spot urine assessments (or discarded):

  - ***All*** subsequent urine voids through up to 0H on Day 1 (in the case of baseline with collection started at time-matched 0H on Day -1) ***and*** 24 hours post dose (on Day 14) will be collected and saved in a container and stored in refrigerated conditions (ie, 2-8°C) for the duration of the collection interval.

- ***Each*** interval urine collection ***will end*** (ie, at 12H and 24H) with a forced void which is *included* as part of the interval urine collection:

  - If the end of the urine collection interval coincides with a meal, participants will be asked to complete the forced void prior to initiation of the meal;

  - In such cases, as long as the actual time of forced void is recorded, for practical reasons, the fact that this collection may be more than 30 minutes (and up to 45 minutes) prior to end of collection interval is acceptable and will not be considered as a protocol deviation.

- The urine will be mixed, and the total volume and weight will be recorded (for the intervals of 0-12H and 0-24H);

- CCI [redacted]

  [redacted]

- CCI [redacted]

  [redacted]

  [redacted]

  [redacted]

[redacted]

CCI [redacted]

8.9. Immunogenicity Assessments

Immunogenicity assessments are ***not*** included in this study.

8.10. 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 an SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

No formal hypothesis tests are planned for this study.

9.2. Sample Size Determination

Part 1: A sample size of 8 participants per cohort for this single, dose-escalating, 4-period, cross-over, with placebo insertion study (6 active, 2 placebo per dose level) 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 and toleration information at each dose level.

Part 2: A sample size of 10 participants per cohort, with 8 participants randomized to PF-07202954 plus 2 participants to placebo per cohort, has been selected as a compromise between the need to minimize exposure to PF-07202954 and the need to have sufficient participants randomized to provide adequate safety and toleration information, PK, and ability to assess clinical pharmacology of PF-07202954 CCI [redacted] at each dose level.

Part 3 (if conducted): A sample size of 8 (minimum) to 12 (maximum) participants will provide adequate precision to estimate the AUC_{inf} of PF-07202954 when it is administered with a high-fat/high-caloric meal (Test condition) as compared to PF-07202954 administered following an overnight fast (Reference condition). This sample size assumes that the

within-participant SD for log-transformed PK parameters would not increase beyond approximately 0.24. The probable 90% CI[21] with 80% coverage probability for an effect size of 1.0 (ie, no change in exposure with and without food) for a range of SDs and sample sizes are provided in Table 6. The sample size ultimately decided for Part 3, by the sponsor, will depend on observed variability in plasma PK observed in Part 1.

Table 6. Probable 90% CI with 80% coverage probability for Varying SDs and Sample Sizes – in Part 3

Sample Size	SD = 0.18	SD = 0.21	SD = 0.24
8	0.81 – 1.23	0.78 – 1.28	0.76 – 1.32
10	0.84 – 1.19	0.81 – 1.23	0.79 – 1.26
12	0.86 – 1.17	0.84 – 1.20	0.81 – 1.23

A total of up to 88 unique participants (16 in Part 1, initially 30-40 with expansion up to 50 [with 5 cohorts] or 60 [with 6 cohorts] in Part 2, and a maximum of 12 in Part 3) are planned to be randomized in this study. Participants discontinuing prior to completion of the study ***for reasons other than safety*** may, at the discretion of the investigator and sponsor, be replaced by another participant who will –

- ***If in Part 1***, repeat all 4 Periods; but in ***rare*** circumstances, as guided by the need to ensure collection of sufficient placebo data, including within participant placebo-comparison, a decision *may* be made for the replacement participant to complete some and not all 4 Periods;

- ***If in Part 2 or Part 3***: repeat all dosing periods (ie, 14 days of dosing in Part 2 *and* both Periods in Part 3) in order to ensure interpretable data.

9.3. Analysis Sets

For purposes of analysis, the analyses sets are defined as outlined in Table 7.

Table 7. Definition of the Analyses Sets in Study C4171001

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization: • Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention for the given Part (1, 2, or 3).
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK Concentration	All participants who receive at least 1 dose of PF-07202954 and in whom at least 1 PK concentration is reported, for the given Part (1, 2, or 3).
PK Parameter	All participants who receive at least 1 dose of PF-07202954 and who have at least 1 of the PK parameters of interest calculated, for the given Part (1, 2, or 3).

9.4. Statistical Analyses

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

9.4.1. General Considerations

The data from each of the 3 Parts will be analyzed and reported separately in a single CSR issued at the end of this study.

9.4.2. Primary Endpoint(s)

The primary endpoints in Part 1 and Part 2 are related to safety/tolerability with analyses as described in Section 9.4.5.

The primary endpoints in Part 3 are the plasma PK endpoints whose analyses are described in Section 9.4.3.1 and Section 9.4.3.2.

9.4.3. Secondary Endpoint(s)

The secondary endpoints (in Part 1 and Part 2) as well as the primary endpoints (in Part 3) related to PK are described herein.

9.4.3.1. PK Analysis

9.4.3.1.1. Derivation of PK Parameters

The PK parameters for PF-07202954 following oral dose administration will be derived from the concentration-time profiles as detailed in Table 8 [following single doses in Part 1 and Part 3] and Table 9 [following single and repeated doses in Part 2].

In all cases, actual PK sampling times will be used in the derivation of PK parameters.

Table 8. Plasma PK Parameters for Part 1 (*Single*, Escalating Doses) and Part 3 (Single Dose Food Effect, *if Conducted*)

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
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 observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
T_{lag}	Lag time	Observed directly from data as time prior to the time corresponding to the first quantifiable concentration.

Table 8. Plasma PK Parameters for Part 1 (*Single*, Escalating Doses) and Part 3 (Single Dose Food Effect, *if Conducted*)

Parameter	Definition	Method of Determination
$t_{1/2}$*	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve: • Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F*	Apparent clearance	$Dose/AUC_{inf}$
V_z/F*	Apparent volume of distribution	$Dose/(AUC_{inf}\ k_{el})$
CCI [redacted]	[redacted]	[redacted]

*As data permit

Table 9. Plasma and Urine PK Parameters for Part 2 (*Repeated* Escalating Doses)

Parameter	Day(s)	Definition	Method of Determination
Plasma			
AUC_{tau}	1, 7, 14	Area under the plasma concentration-time profile from time 0 to time τ (tau)	Linear/Log trapezoidal method
C_{max}	1, 7, 14	Maximum observed concentration during the dosing interval	Observed directly from data
T_{max}	1, 7, 14	Time for C_{max}	Observed directly from data as time of first occurrence
T_{lag}	1, 7, 14	Lag time	Observed directly from data as time prior to the time corresponding to the first quantifiable concentration
C_{min}	7, 14	Minimum observed concentration during the dosing interval	Observed directly from data
C_{av}	7, 14	Average concentration	AUC_{tau}/tau
PTR	7, 14	Peak-to-trough ratio	C_{max}/C_{min}
$R_{ac,AUCtau}$	7, 14	Observed accumulation ratio	AUC_{tau} (Day 7 or 14)/AUC_{tau} (Day 1)
$R_{ac,Cmax}$	7, 14	Observed accumulation ratio for C_{max}	C_{max} (Day 7 or 14)/C_{max} (Day 1)
$t_{1/2}$*	14	Terminal half-life	$Log_e(2)/k_{el}$, • where k_{el} is terminal phase rate constant calculated by a linear regression of log-linear concentration-time curve. • only those data points judged to describe terminal log-linear decline will be used in the regression.
V_z/F*	14	Apparent volume of distribution	$Dose/(AUC_{tau}\ k_{el})$
CL/F	7, 14	Apparent clearance	$Dose/AUC_{tau}$
CCI [redacted]	[redacted]	[redacted]	[redacted]
Urine			
Ae_{tau}	14	Amount of unchanged drug recovered in urine during dosing interval	Sum of [urine concentration x urine volume] for each collection over the dosing interval
Ae_{tau}%	14	Percent of dose recovered in urine as unchanged drug over dosing interval	100 x Ae_{tau}/Dose
CL_r	14	Renal clearance	Ae_{tau}/AUC_{tau}

9.4.3.2. Statistical Methods for PK Data

No formal inferential statistics will be applied to the plasma PK data from Part 1 and 2. In Part 3, if conducted, the statistical comparison of plasma PK under high-fat/high-caloric state (test) versus fasted (reference) condition is envisioned.

- ***Part 1 (Single, Escalating Doses):*** Plasma concentrations of PF-07202954 will be descriptively summarized and plotted by nominal PK sampling time and dose:
  - The plasma PK parameters AUC_{inf}, C_{max}, AUC_{last}, T_{max}, T_{lag}, CL/F, V_z/F, and $t_{½}$ will be summarized descriptively by dose;

  [redacted]

  [redacted]

- ***Part 2 (Repeated, Escalating Doses):*** Plasma concentrations of PF-07202954 will be descriptively summarized and plotted by nominal PK sampling time, day, and dose:
  - The plasma PK parameters AUC_{tau}, C_{max}, T_{max}, T_{lag}, $t_{½}$, C_{min}, C_{av}, PTR, CL/F, V_z/F, $R_{ac,AUCtau}$, and $R_{ac,Cmax}$, and the urine PK parameters Ae_{tau}, Ae_{tau}%, and CL_r will be summarized descriptively by dose and day as applicable;

  [redacted]

  - Median morning trough (predose) plasma concentrations will be plotted by day (all doses on the same plot) in order to assess the attainment of steady state.

- ***Part 3 (Single-Dose Food Effect, if conducted):*** To compare PF-07202954 exposures following high-fat/high-caloric meal (Test) versus following an overnight fast (Reference) natural log-transformed C_{max}, AUC_{last}, and AUC_{inf} (if data permit) will be analyzed using a mixed effects model with treatment as a fixed effect and participant as a random effect. Period may also be included as a factor in the model. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

- ***In addition*** –
  - Plasma concentrations of PF-07202954 will be descriptively summarized and plotted by nominal PK sampling time and treatment;
  - The plasma PK parameters AUC_{inf}, C_{max}, AUC_{last}, T_{max}, T_{lag}, CL/F, V_z/F, and $t_{½}$ will be summarized descriptively by treatment;
  - For AUC_{inf}, C_{max}, and AUC_{last}, box and whisker plots will be presented by treatment and overlaid with geometric means.

CCI

CCI [redacted]

a. For a complete definition of all PK parameters refer to Table 8 and Table 9.

NOTE: For all non-PK related endpoints, ***baseline is defined*** as the time-matched data obtained while on placebo [Part 1], 0H assessment on Day 1 or 0-12H or 0-24H assessment prior to 1st dose [Part 2], ***or*** 0H assessment on Day 1 in *each* Period [Part 3], unless otherwise specified in the SAP.

9.4.4.1. Analysis of Measures of Clinical Activity

For these analyses, the ***Evaluable Set*** as defined in Table 7 will be utilized.

Description of the analyses for the tertiary endpoints (refer to Table 10) will be outlined in the SAP.

9.4.5. Safety Analyses

9.4.5.1. Standard Safety Analyses

In this study, assessment of safety and tolerability following single- and repeated-, escalating doses forms the primary objective for Part 1 and Part 2. In all 3 Parts of the study, all safety analyses will be performed on the ***Safety Analysis Set***.

All 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, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and PE 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.

9.4.5.2. 12-lead ECG Interval Analyses

Changes from baseline for the ECG parameters QT interval, HR, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum post dose QTcF values and maximum increases from baseline in the categories outlined in Table 11 will be tabulated by treatment.

Table 11. Safety QTcF Assessment in Study C4171001

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

When 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 timepoint. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the post dose QTcF value and the average of the time-matched baseline triplicate values while on Placebo (in Part 1), the average of the triplicate collected at 0H prior to dosing on Day 1 (in Part 2), ***or*** the predose value on Day 1 in *each* Period (in Part 3).

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.

CCI [redacted]

9.5. Interim Analysis

As guided by observed safety/tolerability, PK, CCI [redacted] of clinical activity, in Part 1 and Part 2 in this study, a formal interim analysis may be considered to evaluate potential revision to the currently proposed AUC_{24} PK stopping limit in Part 2 (ie, AUC_{24}=3,680 ng•h/mL). This interim analysis will be used to evaluate whether repeated, escalating doses of PF-07202954 doses yielding exposures greater than the currently planned PK stopping limit in Part 2 are attempted. If data are supportive, studying higher exposures will be contingent on a protocol amendment which will undergo the required regulatory and

EC/IRB approvals. Before the interim analysis is instigated, the details of the objectives, the method of maintaining the study blind, and the analyses details will be documented in the SAP and/or IA charter.

As this is a sponsor-open study, a limited number of the sponsor's team members (excluding site staff) may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will *not* use a DMC.

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 and 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.

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 guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study 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, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

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

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

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

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 his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

Monitoring details describing strategy (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, remote, or on-site monitoring), are provided in the IQMP.

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

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

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the Source Document Locator.

Description of the use of computerized system is documented in the Source Document Locator.

10.1.8. Study and Site Start and Closure

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

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

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

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the CTMS.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Table 12 delineates the protocol mandated safety-related laboratory tests CCI [redacted] of clinical activity to be collected following ***an overnight fast of ≥10 hours***, *unless otherwise specified*, at timepoints defined in the SoA-Table A, SoA-Table B, SoA-Table C, and SoA-Table D.

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.

Investigators must document their review of *each* laboratory safety report.

Laboratory/analyte results that could unblind the study will ***not*** be reported to investigator sites or other blinded personnel until the study has been unblinded.

Table 12. All Planned Protocol-Required Safety-Related Laboratory Tests CCI [redacted] in Study C4171001

Hematology	Chemistry	Urinalysis
– Hemoglobin – Hematocrit – RBC count – MCV – MCH – MCHC – Platelet count – WBC count – Total neutrophils (Abs) – Eosinophils (Abs) – Monocytes (Abs) – Basophils (Abs) – Lymphocytes (Abs) – Reticulocytes (Abs)	– BUN – SCr (and eGFR using CKD-EPI) CCI [redacted] – Calcium – Sodium – Potassium – Chloride – Total CO_2 (bicarbonate) – AST (SGOT) – ALT (SGPT) – TBili – ALP – GGT – Direct (conjugated) bilirubin – Indirect (unconjugated) bilirubin – Creatine Kinase[b] – Uric acid – Albumin – Total protein	– pH – Glucose (qual) – Protein (qual) – Blood (qual) – Ketones – Nitrites – Leukocyte esterase – Urobilinogen – Urine bilirubin – UACR – UPCR – Microscopy[a]
Other		
• **At Screen, only,** in all 3 Parts – – Serum FSH;[c] – HBsAg, HBcAb, HCVAb, HIV. • Serum pregnancy test (in ***all*** females; refer to Section 8.2.5). • Urine drug test.[d]		

Table 12. All Planned Protocol-Required Safety-Related Laboratory Tests CCI [redacted] in Study C4171001

CCI [redacted]	
Additional Tests for instances of suspected Hy's Law [refer to Section 10.6]:	
– ALT, AST (repeat) – TBili (repeat) – Albumin (repeat) – ALP (repeat) – Direct bilirubin – Indirect bilirubin	– CK – GGT – PT/INR – Total bile acids – Acetaminophen drug and/or protein adduct levels

a. ***In Part 1 and Part 3*** to be performed ***only if*** urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase; however, ***in Part 2 only,*** to be performed at all timepoints ***irrespective*** of results on urine dipstick (as it related to blood, protein, nitrites, or leukocyte esterase).
b. Test to be assessed upon ***each*** admission (in Part 1, Part 2, and Part 3); ***but*** after initiation of study intervention, ***only*** when ALT *or* AST is >ULN.
c. In females amenorrhoeic ≥12 months, ***only***, for confirmation of postmenopausal status *only.*
d. *Minimum* requirements for urine drug test includes cocaine, opiates/opioids, benzodiazepines, and amphetamines.

For list of terms corresponding to the abbreviations used herein, refer to Section 10.8.

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 CCI [redacted] or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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

10.3.1. Definition of AE

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

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

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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
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 detained (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 disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. 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, and occupational exposure	• All AEs/SAEs associated with exposure during pregnancy or breastfeeding. • Occupational exposure is ***not*** recorded.	All (and EDP supplemental form for EDP). ***Note:*** Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/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/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/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not

the individual signs/symptoms) will be documented as the AE/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:*** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- ***Moderate:*** An event that causes sufficient discomfort and interferes with normal everyday activities.
- ***Severe:*** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality**

for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study ***or*** during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data

become available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.

- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

- Is *not* a WOCBP (see definitions below in Section 10.4.3);

OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition,
        - 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.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency [female participants *and* female 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.

6. Sexual abstinence.

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

Highly Effective Methods [female partners of male participants, *only*]

1. **Highly Effective Methods That Are User Dependent** Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation.

    - Oral;

    - Injectable.

3. 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 ***male*** participant.

One of the following effective barrier methods must be used ***in addition*** to the highly effective methods listed above that are user dependent:

- 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, **blood samples** will be collected for DNA analysis.

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

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07202954/placebo 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 8.7.1) will be stored for ***up to 3 years*** after regulatory approval *or* other period as per local requirements, unless the study participant signs the Additional Consent Request permitting longer storage for optional additional research.

    - Samples for banking 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 Banked Biospecimens 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.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

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 an “adaptor” or are “susceptible.”

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, 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 and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

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

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

10.8. Appendix 8: Abbreviations

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

Abbreviation	Term
Abs	absolute
AE	adverse event
AESI	adverse events of special interest
Ae_{tau}	amount of unchanged drug recovered in urine during the dosing interval
Ae_{tau}%	percent of dose recovered in urine as unchanged drug over the dosing interval
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{12}	area under the curve over the time of 0-12 hours post dose
AUC_{24}	area under the curve over the time of 0-24 hours post dose
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration
AUC_{tau}	area under the plasma concentration-time profile from time 0 to time τ (tau), the dosing interval
$AUEC_{24}$	area under the effect curve over the time of 0-24 hours post dose
AV	atrioventricular
BBS	Biospecimen Banking System
BCRP	Breast cancer resistance protein
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CAP™	Controlled attenuation parameter (trademarked by EchoSens®)
C_{av}	average concentrations
CBP	childbearing potential
C_{eff}	projected human effective plasma concentration
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
CL/F	apparent clearance
C_{last}	Last quantifiable plasma concentration
CL_{plasma}	plasma clearance
CL_r	renal clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed concentration
CNS	Central nervous system
CO_2	carbon dioxide (bicarbonate)
COVID-19	Coronavirus Disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial

Abbreviation	Term
CTA	Clinical Trial Application
CTMS	clinical trial management system
CV	Cardiovascular
CYP	cytochrome P450
CCI	[redacted]
D/C	Premature discontinuation of participation post dosing on Day 1 from study
DAG	diacylglycerol
DCT	data collection tool
DDI	drug-drug interaction
DGAT	diacylglycerol acyltransferase
DGAT2i	diacylglycerol acyltransferase-2 inhibitor
DILI	drug-induced liver injury
DMC	data monitoring committee
CCI	[redacted]
DNA	deoxyribonucleic acid
DNL	de novo lipogenesis
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
ED_{50}	effective dose for 50% of the population
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
EFD	Embryofetal development
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
E_{max}	maximum response achievable
EU	European Union
EudraCT	European Clinical Trials Database
F	oral bioavailability
FAMHP	Federal Agency for Medicines and Health Products
FDA	Food and Drug Administration
FFA	free fatty acid
FIH	first-in-human
FSH	follicle-stimulating hormone
fu	fraction unbound
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCVAb	hepatitis C antibody
hDGAT	human diacylglycerol acyltransferase
HDL-C	high-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
CCI	[redacted]
HR	heart rate
HRT	hormone replacement therapy

Abbreviation	Term
IA	interim analysis
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
IC_{85}	maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
IND	investigational new drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IQMP	integrated quality management plan
IRB	institutional review board
IV	intravenous
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
k_a	acid dissociation constant
K_{el}	terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
CCI	[redacted]
LBBB	left bundle branch block
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
Log_e	logarithm to the base of the mathematical constant e
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR1	multidrug resistance protein 1
MGAT	monoacylglycerol acyltransferase
MR	magnetic resonance
CCI	[redacted]
mRNA	messenger ribonucleic acid
N/A	not applicable
NAFLD	nonalcoholic fatty liver disease
CCI	[redacted]
NASH	nonalcoholic steatohepatitis
CCI	[redacted]
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OAT1	organic anion transporter-1
OAT3	organic anion transporter 3
OCT2	organic cation transporter 2
PBPK model	physiologically-based pharmacokinetic model
PCRU	Pfizer clinical research unit
CCI	[redacted]
PD	pharmacodynamic(s)
PE	physical examination
P-gp	P-glycoprotein
PGx	pharmacogenomic(s)
pH	potential of hydrogen
PI	Principal Investigator
PK	pharmacokinetic(s)

Abbreviation	Term
pKa	Negative log of the acid dissociation constant
PR interval	interval between the start of the electrocardiogram P wave and start of QRS complex, corresponding to time between onset of atrial depolarization and onset of ventricular depolarization
PT	prothrombin time
PTR	peak-to-trough ratio
PVC	premature ventricular contraction/complex
QRS	combination of 3 graphical deflections seen on a typical electrocardiogram
QT	time from electrocardiogram Q wave to end of T wave corresponding to electrical systole
QTc	corrected time from electrocardiogram Q wave to end of T wave corresponding to electrical systole
QTcF	corrected time from electrocardiogram Q wave to end of T wave corresponding to electrical systole (Fredericia method)
qual	qualitative
R_{ac}	observed accumulation ratio
RBC	red blood cell
RNA	ribonucleic acid
RRCK	Ralph Russ Canine Kidney cell-based permeability assay
SAE	serious adverse event
SAP	statistical analysis plan
SAR-CoV2	Severe acute respiratory syndrome-coronavirus 2
SCr	serum creatinine
CCI	[redacted]
SD	standard deviation
SGOT	serum glutamic oxalo-acetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoA	Schedule of Activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
TBili	total bilirubin
TG	triglyceride(s)
T_{lag}	lag time
T_{max}	time to achievement of maximum plasma concentration
UACR	urinary albumin-to-creatinine ratio
ULN	upper limit of normal
UPCR	urinary protein-to-creatinine ratio
US	United States
US FDA	United States Federal Drug Administration
UV	Ultraviolet
VCTE™	Vibration-controlled transient elastography (trademarked by EchoSens®)
VLDL	very low density lipoprotein
VLDL-C	very low density lipoprotein cholesterol
V_{ss}	steady state volume of distribution
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential

11. REFERENCES

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