A PHASE 1B, RANDOMIZED, DOUBLE-BLIND (SPONSOR-OPEN), PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACODYNAMICS AND PHARMACOKINETICS OF MULTIPLE ORAL DOSES OF PF-06865571 FOR 2 WEEKS IN ADULTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Investigational Product Number:	PF-06865571
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	C2541005
Phase:	1b

[redacted]

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	27 February 2018	N/A

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

LIST OF FIGURES

APPENDICES

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to Section 6 and Section 7 of the protocol for additional information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Overall Visit Schedule and List of Procedures

Protocol Activity	Screening			Day -2	Study Day (all activities at 0H [prior to dosing] unless otherwise specified)[a]																Follow-up[b]	
Days Relative to Dosing on Day 1	Screen 1	Screen 2	Screen 3		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Visit	Contact
Visit	1	2	3	4																		5	-
Informed consent & demography	x																						
Outpatient visit (after ≥8H fast)	x																					x	
Adverse event monitoring	x			x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x	x
Inpatient stay at CRU				x[c]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x		
Medical & medication history	x			x																		x	x
Review drug, alcohol/tobacco use	x			x																		x	
Review prior or concomitant treatments	x			x																		x	
Review contraception use	x			x																		x	x
Physical examination (height at Screen 1 only)[d]	x			x																x			
Body weight	x			x					x						x					x		x	
Triplicate, supine 12-lead ECG[e]	x								x						x						x	x	
Single, supine vital signs assessment[e]	x								x						x						x	x	
Liver fat and stiffness (via FibroScan®)[ff]	x	x		CCI																			
Liver fat via MRI-PDFF acquisition[f,g]			x	x	Refer to Tabl	Refer to Tabl						Refer to Tabl							Refer to Tabl	x			
Standardized meals/snacks[h]				x			x	x	x	x	x		x	x	x	x	x	x		x	x		
Administration of blinded IP[i]							x	x	x	x	x		x	x	x	x	x	x					
Blood sampling for:																							
- Clinical laboratory tests and serum cystatin C[j]	x								x						x						x	x	
- Serum FSH (females only), HIV, HepBsAg, HepBcAb, HCVAb testing	x																						
- Ceruloplasmin, A1AT, HbA1c	x																						
- PF-06865571 PK[k]									x				x							x			
- Serum TG																				x			
CCI																							
- Plasma insulin[j]	x								x						x							x	
CCI																							

Protocol Activity	Screening			Day -2	Study Day (all activities at 0H [prior to dosing] unless otherwise specified)[a]															Follow-up[b]	
Days Relative to Dosing on Day 1	Screen 1	Screen 2	Screen 3		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Visit	Contact
Visit	1	2	3	4																		5	-
Urine sampling for:																							
- Urine drug test	x																						
- Urinalysis (and microscopy, as appropriate)	x								x						x						x	x	

a. Day relative to start of dosing of blinded investigational product (Day 1).

b. Follow-up visit at 7-10 days following the last dose will be an outpatient visit to the site, while follow-up contact at 28-35 days following the last dose may occur via a follow-up phone call. Phone call may be a visit if deemed necessary by the investigator.

c. Admission to CRU should occur prior to lunch on Day -2.

d. Full physical exam at Screen 1 and at Day 15; otherwise, limited exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.

e. Prior to AM dose.

f. After ≥8H fast at outpatient visits; scans on Days -2 & 15 to occur post overnight fast of ≥8H at approximately same clock time (ie, within a practical window (±2 hours) relative to clock time of the Screening visits). CCI [redacted]

g. At Screen 3 visit **after** confirmation of ***all*** other eligibility.

h. Meals to be provided at approximately 0H, 4H, and 10H post AM dose and snack to be provided at approximately 12H post AM dose, as specified in Section 4.4.1. Day 16 meal(s) are optional, according to clinical research unit (CRU) practice.

i. Dosing to occur with breakfast and snack, as specified in Section 4.4.1.

CCI [redacted]

k. PK samples to be collected prior to dose.

[redacted]

Table 2. Schedule of Activities – Study Days -1, 1, 7 & 14

[Procedures at 0H to be completed prior to dosing or similar clock time, in the case of Day -1]

Hours Relative to Dosing at 0H[a]	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**24**
Continued inpatient stay at CRU	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse event monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Body weight	x													
Triplicate, supine 12-lead ECG	x													
Single, supine vital sign assessment	x													
Blinded IP administration (Days 1, 7 and 14 only)	x[b]									x[c]				
Randomization (Day 1 only)	x													
Blood sampling for:														
- Clinical laboratory tests and serum cystatin C[d] (Days 1, 7, and 14 only)	x													
CCI														
- PF-06865571 PK (Day 14 only)	x		x	x	x	x	x	x		x				
- Serum triglycerides (Days -1, 1 and 14 only)[d]	x[f]			x		x	x	x	x	x	x	x	x	
CCI														
- Plasma insulin[d,g]	x													
Urine sampling for:														
- Urinalysis and microscopy, as appropriate (Days 1, 7, and 14 only)	x													
Meals[h]														
- Standardized meal	x					x			x					
- Snack										x				

a. On Day -1, nominal time to approximately match clock time of collection planned on Day 1 to permit time-matched comparison.

b. Dosing expected to occur with breakfast.

c. Dosing expected to occur with snack as specified in Section 4.4.1.

CCI

g. Insulin samples collected in triplicate on Day -1 and Day 14. On Day 1 and Day 7, only 1 sample will be collected.

h. Meals/snacks to occur on all days while inpatient; identical meals/snacks on Days -2, -1, 1, 14, and 15.

1. INTRODUCTION

Diacylglycerol acyltransferases (DGATs) catalyze the terminal step in triglyceride (TG) synthesis; specifically, the esterification of a fatty acid (FA) with diacylglycerol (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] DGAT2 is highly expressed in liver and adipose.[3] In preclinical models, blockade of hepatic DGAT2 using antisense oligonucleotides results in both down-regulation of the expression of multiple genes encoding proteins involved in lipogenesis and parallel induction in oxidative pathways.[4,5] The net result of these changes is a decrease in the levels of hepatic DAG and TG lipid which, in turn, reduces hepatocyte lipid burden and decreases hepatic very low density lipoprotein (VLDL) TG secretion.[5,6] PF-06865571 is an oral, small molecule DGAT2 inhibitor that is postulated to decrease hepatic TG synthesis and hepatic lipid burden in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

The current study is the first designed to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) following administration of repeated (up to 14 days) oral doses of PF-06865571 in the fed state to adult subjects with NAFLD.

1.1. Mechanism of Action/Indication

PF-06865571 is an oral, small molecule DGAT2 inhibitor that is currently being developed for the treatment of NASH.

1.2. Background

NAFLD is estimated to affect at least 25% of the general population in Western countries, while the prevalence of NASH is estimated at 3 to 5%.[7] NAFLD is strongly associated with obesity, insulin resistance, hypertension, and dyslipidemia and is now regarded as the hepatic manifestation of metabolic syndrome.[8] NAFLD describes a spectrum of liver conditions whose dominant feature is hepatic TG accumulation.[9] NASH is diagnosed clinically by liver biopsy demonstrating steatosis, inflammation, and ballooning of liver hepatocytes, often with varying degrees of fibrosis. NASH progresses with increasing degrees of fibrosis, with cirrhosis and/or hepatocellular carcinoma developing in a subset of patients.[10] Although the factors that promote TG deposition in the liver and transition from steatosis to NASH and cirrhosis in humans have not been clearly defined, hepatic steatosis arises from an imbalance between TG acquisition and removal.[11] Although there is a growing body of evidence that demonstrates the urgent need for therapies for NASH, there are no currently approved therapies for the treatment of NASH.[10]

Hepatic TGs are derived from 3 principal sources: de-novo lipogenesis (DNL), re-esterification from FA supplied by the adipose, and dietary intake.[11] While the largest contribution to the hepatic TG pool appears to be derived from lipolytic products originating in adipocytes, the lipogenic pathway plays an important role in the development of NAFLD and progression to NASH.[12] The contribution of DNL to disease progression in NAFLD is supported by analyzing the FA composition of TGs in subjects with and without NAFLD. Data demonstrate an increased level of saturated FAs in those with NAFLD, implicating the

DNL pathway as an important contributor to hepatic steatosis as saturated FAs represent the primary product of DNL.[12] These findings are consistent with the increased inclusion of DNL-derived TGs in VLDL particles in NAFLD where 15% of TG produced originated from DNL compared to only 2 to 5% in normal subjects consuming a typical Western diet.[12] Additionally, elevated rates of hepatic DNL have been reported to be a distinctive characteristic of NAFLD.[13] Human subjects with elevated liver fat showed a more than 3-fold increase in the rate of hepatic DNL relative to subjects with normal liver fat, but no differences between the groups were detected in adipose free fatty acid (FFA) flux or in production of VLDL from FFAs. Consequently, when comparing the absolute sources of FAs incorporated into VLDL-TG, elevated hepatic DNL was the only source significantly elevated in subjects with high liver fat.[13]

Based on observations in nonclinical studies conducted with PF-06865571, it is hypothesized that DGAT2 inhibition 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.

1.2.1. Nonclinical Primary Pharmacology

1.2.1.1. In Vitro Assays

PF-06865571 is a potent and selective inhibitor of human DGAT2 (hDGAT2). CCI [redacted] The selectivity of PF-06865571 for DGAT2 was supported by in vitro studies demonstrating >2000-fold selectivity by biochemical assessment versus related acyltransferases including recombinant human DGAT1 (hDGAT1), monoacylglycerol acyltransferase (MGAT)2 and MGAT3, as well as mouse MGAT1. C
CI [redacted]

1.2.1.2. In Vivo Studies

Following single dose administration, PF-06865571 demonstrates robust, dose-dependent reduction of plasma triacylglycerol in rats fed a high sucrose-diet. In longer term studies in Western diet fed rats, PF-06865571 reduces both plasma triacylglycerol and hepatic lipid accumulation. In line with the proposed mechanism of action, administration of PF-06865571 in both sucrose and Western diet fed rats results in suppression of key genes involved in hepatic lipid metabolism, including the messenger ribonucleic acid (mRNA) expression of proprotein convertase subtilisin/kexin type 9 (PCSK9). In these nonclinical models dosed with PF-06865571, PCSK9 mRNA was decreased relative to vehicle treated animals by 55% and 84% in the Western and sucrose-diet models, respectively.

1.2.2. Nonclinical Pharmacokinetics and Metabolism

Nonclinical data indicate that PF-06865571 has high passive permeability and is a substrate for multi-drug resistance protein 1 (MDR1, also known as P-glycoprotein or P-gp) and

mouse breast cancer resistant protein (mBCRP) efflux transporters. PF-06865571 was rapidly absorbed in rat and moderately absorbed in the monkey with a mean oral bioavailability of 31% and 48%, respectively.

Urinary excretion (rat and monkey) of unchanged drug was ≤1%, while biliary excretion of unchanged drug was <1% when assessed in bile duct cannulated rats.

PF-06865571 was moderately bound to plasma proteins in rat, monkey, and human with average fraction unbound (fu) ranging from 0.213 to 0.419, and preferentially distributes into plasma relative to blood with blood to plasma concentration ratio ranging between 0.659 and 0.901. The major clearance mechanism of PF-06865571 is predicted to be predominantly by CYP3A mediated metabolism with minor contributions by CYP2B6 and CYP2C19.

There is no evidence of human-unique metabolites, and all metabolites detected in human cryopreserved hepatocytes were also observed in the nonclinical toxicology species (rat and monkey). Reaction phenotyping studies indicate the total cytochrome P450 (CYP450) contribution to PF-06865571 metabolism was >96% and CYP3A is the predominant isoform responsible for the metabolism of PF-06865571. Modeling suggests a moderate risk of clinical drug-drug interactions (DDIs) with PF-06865571 as a victim upon co-administration with CYP3A4 inhibitors or inducers.

Assessment of the DDI potential for PF-06865571 on selected CYP and UDP glucuronosyltransferase (UGT) enzymes and drug transporters is based on the predicted mean steady-state unbound C_{max} of 555 ng/mL (~1.36 μM) corresponding to the highest dose of PF-06865571administered in the current study (300 mg Q12H)). PF-06865571 mediated DDIs resulting from inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2D6, and CYP3A4/5 are not expected; however, PF-06865571 does have the potential to inhibit CYP2C9 and CYP2C19 at clinically relevant concentrations. It is unlikely PF-06865571 will inhibit UDP UGT, 1A4, 1A6, 2B7, and 2B15 enzymes at clinically relevant concentrations; however, PF-06865571 does have the potential to inhibit UGT1A1 and UGT1A9. PF-06865571 demonstrated induction of CYP3A4 and CYP2B6 activity (mRNA and enzymatic) in human hepatocytes. At the anticipated highest dose of PF-06865571 in currently planned clinical trials (300 mg twice daily [BID]), modeling suggests a moderate change in the exposure of CYP3A4 substrates primarily due to intestinal CYP induction. In vitro evaluations indicate that PF-06865571 has a low potential to inhibit organic anion transporter (OAT)1, OAT3, multidrug and toxin extrusion protein (MATE)2K, organic cation transporter (OCT)1, organic anion transporting polypeptide (OATP)1B1, and OATP1B3 at clinically relevant concentrations. However, PF-06865571 does have the potential to inhibit P-gp, breast cancer resistance protein (BCRP), MATE1, and OCT2 at clinically relevant concentrations.

1.2.3. Summary of Toxicology Studies

PF-06865571 was evaluated in vitro and in vivo in genetic toxicity studies and safety pharmacology studies, in vivo in oral repeat-dose rat and monkey toxicity studies up to 6 weeks duration, and in an in vitro phototoxicity assessment. PF-06865571 was not mutagenic or clastogenic in in vitro studies and was negative in in vivo rat micronucleus studies. No significant findings were noted in safety pharmacology in vitro or in vivo in neuropulmonary and cardiovascular studies in rats and monkeys, respectively. No adverse

toxicity and no target organs or systems were identified in Wistar Han rats or cynomolgus monkeys following single or repeat doses (up to 6 weeks) of PF-06865571 via oral gavage administration at doses up to 1000 (500 BID) mg/kg/day. These were maximum feasible doses based on dose volume and formulation limitations. PF-06865571 did not demonstrate phototoxic potential in the neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts.

The no observed adverse effect levels (NOAELs) in the 6-week studies were the highest dose levels tested, 1000 (500 BID) mg/kg/day with associated unbound maximum observed concentration (C_{max}) and area under the curve (AUC_{24}) of 2450/7880 ng/mL and 25300/103000 ng·h/mL (males/females), respectively, in rats, and 4790 ng/mL and 56900 ng·h/mL, respectively, in monkeys. After correction for species differences in protein binding, the stopping criteria in humans are set to a C_{max} of 6940 ng/mL and AUC_{24} of 71670 ng·hr/mL (ie, NOAEL exposures observed in rats).

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the investigator's brochure (IB) for PF-06865571.

CCI

[redacted]

CCI
[redacted]

1.3. Study Rationale

The current study is the first to evaluate the effect of PF-06865571 (compared to placebo) on liver fat, as assessed via magnetic resonance imaging proton density fat fraction (MRI-PDFF), [redacted] The investigational product (IP) will be administered orally for 2 weeks.

1.3.1. Study Design Rationale

Along with an assessment of the effect of PF-06865571 on liver fat, this study is designed to assess the safety and tolerability of 2 different oral dosing regimens of PF-06865571 compared to placebo. To address the potential effect of PF-06865571 on liver fat, the eligible population for study enrollment is subjects with NAFLD, with liver fat ≥6%, as assessed by MRI-PDFF at Screen 3. Subjects who meet all eligibility criteria for the study during Screen 1 (including liver fat approximation by FibroScan®) will then undergo an additional liver fat approximation by FibroScan®at Screen 2. These assessments will provide an initial estimate of liver fat prior to MRI-PDFF. FibroScan® is an ultrasound based technique that estimates liver fat through calculation of the controlled attenuation parameter (CAP™), measured in decibels per meter (dB/m). [redacted]

Subjects who meet all eligibility criteria for the study during Screen 1 and Screen 2 (including liver fat approximation by FibroScan®) will then undergo liver fat assessment by MRI-PDFF at Screen 3. The MRI-PDFF technique is an established method that enables quantification of fat content in the liver. Imaging data are acquired with this method in a manner that accounts for confounding factors that can otherwise result in inaccurate measures of liver fat, while also providing whole-liver coverage such that fat content can be assessed across each of the 9 Couinaud liver segments. This noninvasive methodology has been found to be more sensitive to change in liver fat content than histologically-determined steatosis grade,[14] and has been utilized in previous trials of potential NASH therapeutics.[15,16]

Prior to the assessment of liver fat (CCI MRI-PDFF), subjects will be required to fast (water permitted) for ≥4 hours given the ability of food to impact the imaging results (≥8 hours prior to Days -2 and 15 due to lipid sample collection). Baseline (Day -2) assessments for MRI-PDFF CCI should be at approximately the same clock time (ie, within a practical window (±2 hours) relative to the clock time of the Screening visit). All post-dose assessments CCI MRI-PDFF should occur within a practical window (±2 hours) relative to clock time of each baseline assessment.

Total duration of dosing PF-06865571/placebo in this study is proposed as 2 weeks, as supported by completed nonclinical toxicity studies in rats and monkeys. This duration is also expected to permit sufficient assessment of the primary pharmacology of PF-06865571 and its effect on liver fat. Given the current study is the first to administer repeated doses of PF-06865571 to subjects with NAFLD, a baseline day (Day -1) will permit assessment of safety (including triplicate ECGs) and tolerability, ie, change from baseline (CFB, within subject) and placebo-adjusted comparison of dose-response (between subject), as appropriate.

This study is also designed to assess the effect of PF-06865571 on other PD markers that are intended to provide insight into associated metabolic pathways. CCI

CCI

The serial collection of blood samples to permit assessment of PD effect in this study will assist in understanding the optimal dosing regimen to potentially characterize the dose (or exposure) response, as well as to build PK/PD understanding.

PF-06865571 is not anticipated to have a significant effect on body weight, however, to contain the influence of inpatient stay on liver fat, subjects will have their body weight assessed on serial days and their daily caloric intake adjusted to minimize change (both increase and decrease) in body weight while inpatient – refer to Section 7.1.4.

CCI [redacted]

Creatinine is actively secreted by OCT2/MATE in kidney. In the setting of OCT2/MATE inhibition, serum creatinine levels have been reported to increase slightly.[17] In accordance with reported literature on OCT2/MATE inhibition, minor increases in serum creatinine have been observed in C2541002 with very limited/no change in cystatin. In order to better assess renal function in the setting of possible PF-06865571-induced OCT2/MATE inhibition resulting in spurious serum creatinine increases, serum cystatin C will be assessed as part of the standard safety labs, in addition to serum creatinine, in order to accurately interpret potential changes in glomerular filtration rate (GFR).[18]

1.3.1.1. Study Population

This study will enroll overweight and obese male and female subjects who may be treated for co-existing conditions, such as diet-controlled type 2 diabetes mellitus (T2DM), hyperlipidemia or hypertension, but who are otherwise clinically stable. Female subjects will be confirmed to be categorized as non-childbearing potential since at the present time embryo-fetal developmental toxicology studies with PF-06865571 have not been conducted. In male subjects, appropriate measures to minimize potential transfer of PF-06865571 via semen to a partner are expected to be followed - refer to Section 4.4.4.

Subjects with a higher body mass index (BMI) of ≥28 kg/m^2 will be enrolled to target a similar BMI range as patients with NAFLD and NASH. Subjects with T2DM will be permitted in this study, as long as their glycosylated hemoglobin (HbA1c) is ≤7% and their T2DM is diet-controlled (ie, they do not require oral or injectable medication treatment for T2DM), as there is a potential for PF-06865571 to (1) mildly increase plasma glucose and insulin levels, and (2) raise levels of metformin, a common medication in T2DM, due to OCT2/MATE inhibition. Subjects who use tobacco/nicotine-containing products may also be eligible (see Section 4.4).

The eligible population is defined as having liver fat ≥6% as measured by MRI-PDFF at Screen 3. Although NAFLD is a condition marked by excessive (≥5%) fat accumulation in the liver, this study will enroll subjects with liver fat values ≥6% at screening to allow for potential measurement variability and help ensure baseline liver fat values are likely ≥5%. As it is unknown whether subjects with lower versus higher baseline liver fat values may respond differently to therapy, subjects will be stratified at randomization (Day 1) based on MRI-PDFF (Screen 3) liver fat ranges of ≥6% to <10%; and ≥10% as a means of providing approximate equal balance of liver fat content between the dosing cohorts. A second-tier stratification will also be applied at randomization (Day 1) based on the presence or absence of T2DM (refer to Section 4.3) for additional details.

CCI

1.3.2. Dose Rationale

CCI The dose and dosing regimen required to maximize the PD effects of PF-06865571 are not yet established. CCI In order to fully explore the effect of DGAT2 inhibition on liver fat, PF-06865571 doses of 50 mg and 300 mg will be administered BID in this study. CCI These total daily doses have been well tolerated with an acceptable safety profile in the ongoing multiple ascending dose study (C2541002).

Table 5. Predicted Steady-State PF-06865571 Exposures with Administration of Multiple Doses of PF-06865571 Under Fed Conditions

Total Daily Dose[a] (mg)	Regimen	Predicted C_{max} (ng/mL)	Predicted AUC_{24} (ng•h/mL)
100 mg	50 mg Q12H	430	2198
600 mg	300 mg Q12H	2174	13238

Abbreviations: Q12H = every 12 hours.
a. Predicted C_{max} and AUC_{24} were derived using a preliminary model based on available PK data from Studies C2541001 and C2541002.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoint:**
• To evaluate the effect of multiple oral doses of PF-06865571 on whole liver fat, following 14 days of administration to subjects with NAFLD.	• Relative change from baseline in whole liver fat at Day 15, as assessed by MRI-PDFF.
Secondary Objectives:	**Secondary Endpoints:**
• To evaluate the safety and tolerability of multiple oral doses of PF-06865571, administered for 14 days to subjects with NAFLD.	• Assessment of AEs, clinical laboratory tests, vital signs and 12-lead ECGs.
• To characterize the plasma exposure of multiple oral doses of PF-06865571, administered for 14 days to subjects with NAFLD.	• PF-06865571 C_{max}, AUC_{tau}, T_{max}, C_{min}, CL/F, and PTR on Day 14, as permitted by the data.
CCI [redacted]	

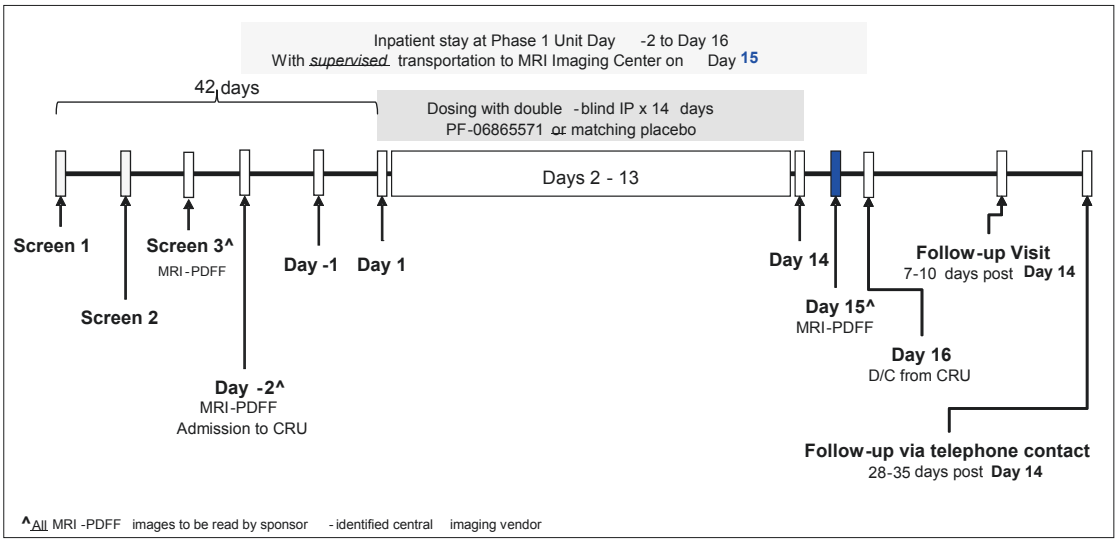
CCI

3. STUDY DESIGN

3.1. Study Overview

This will be a randomized, double-blind (sponsor-open), stratified, placebo-controlled, 3-arm (placebo, plus 2 active doses of PF-06865571), parallel-group study (refer to Figure 1).

Figure 1. Design of Study C2541005



A total of approximately 45 subjects (15 per arm) will be randomized at approximately 4 to 6 sites to ensure a minimum of 42 subjects complete the study (assuming an approximate 5% premature withdrawal rate). Subjects may be replaced at the discretion of the principal investigator (PI) and Sponsor. Subjects will be randomized to receive PF-06865571 (2 dosing regimens) or matching placebo (1 dosing regimen) in a 1:1:1 ratio.

For a given subject, the total study duration from Screen 1 to the follow-up phone call will be up to approximately 13 weeks. Screen 1 will occur within 42 days prior to the first dose of blinded IP (PF-06865571 or matching placebo). Eligible subjects who meet the entry criteria will progress to admission on the morning of Day -2, prior to lunch, for an 18-day (17-night) inpatient stay. While inpatient, subjects will receive blinded IP for 14 consecutive days and remain inpatient for approximately an additional 48 hours post AM dose on Day 14. Following discharge on Day 16, subjects will return for an on-site follow-up visit 7 to 10 days following the last dose of blinded IP, and a follow-up phone call (or visit, if necessary per the PI) 28 to 35 days following the last dose of blinded IP.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Male subjects or female subjects of non-childbearing potential between the ages of 18 and 65 years, inclusive, at Screen 1.

   Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status should be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

   All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

2. At Screen 1, total body weight of >50 kg (110 lbs) and a BMI ≥28 kg/m^2;

3. At ***both*** Screen 1 and Screen 2, a CAP^{TM} ≥260 dB/m via FibroScan® assessment. Note: if the CAP^{TM} value is in the range of 240-259 dB/m, the FibroScan® assessment may be repeated on a different day following at least a 4-hour fast; thus 2 assessments (at least 1 of Screen 1 and repeat Screen 1, ***plus*** at least 1 of Screen 2 and repeat Screen 2) are required to be met above threshold ***before progressing*** to Screen 3;

4. At Screen 3, liver fat ≥6% measured by MRI-PDFF acquisition protocol at the Sponsor-qualified Imaging facility, confirmed via a single repeat, if deemed necessary by the Sponsor-identified central imaging vendor (refer to Section 7.5.1);

5. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study;

6. Subjects who are willing and able to comply with all scheduled visits, clinical research unit (CRU) confinement, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects currently experiencing any clinically significant or unstable medical condition that might limit their ability to complete the study, to comply with the requirements of the protocol, or interfere with the interpretation of study results which, in the judgment of the investigator, would make the subject inappropriate for entry into this study, including: dermatologic disease, hematological disease, pulmonary disease, hepatic disease, gastrointestinal disease, genitourinary disease, endocrine disease, neurological disease and psychiatric disease;

2. Subjects with any of the following clinical laboratory abnormalities at Screen 1, as assessed by sponsor-identified central laboratory and confirmed by a single repeat, if deemed necessary:

    - Fasting TG >400 mg/dL;
    - Fasting direct LDL-C >190 mg/dL;
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma glutamyl transferase (GGT) >2.0 x upper limit of normal (ULN);
    - HbA1c >7.0%;
    - Total bilirubin >1.5x ULN **with a** direct bilirubin ≥ULN;

- NOTE: Subjects with a history of Gilbert syndrome would be eligible for this study provided direct bilirubin level is ≤ ULN **plus** ALT met criteria for applicable 1st tier stratification **plus** alkaline phosphatase, hemoglobin, and reticulocyte count are ≤ ULN.

- Albumin < lower limit of normal (LLN);

- International normalized ratio (INR) ≥1.3.

3. A positive urine drug test for illicit drugs at Screen 1.

   - NOTE: Subjects who have been medically prescribed opiates/opioids or benzodiazepines and report the use of these drugs to the investigator at Screen 1 may be allowed to participate if approved by the sponsor.

4. History of regular alcohol consumption exceeding 14 drinks/week for female subjects or 21 drinks/week for male subjects (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within the previous 6 months from Screen 1;

5. At Screen 1, supine systolic blood pressure (BP) ≥160 mmHg and/or diastolic BP ≥100 mmHg after ≥5 minutes of rest;

   - If needed, the BP may be repeated 2 more times and the average of the 3 BP values will be used to determine the subject's eligibility.

6. At Screen 1, triplicate supine 12-lead ECG (average) demonstrating a QTcF interval >450 msec or a QRS interval >120 msec;

   - 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 subject's eligibility.

7. At Screen 1, subjects with an estimated GFR <60 mL/min/1.73m^2 as calculated by the modification of diet in renal disease equation (MDRD), and confirmed via a single repeat, if deemed necessary.

8. Evidence or diagnosis of other forms of chronic liver disease, including but not limited to the entities listed below; evidence may include laboratory tests, as assessed by the Sponsor-identified central laboratory, with a single repeat at Screen 1 permitted to assess eligibility, if needed:

   - Hepatitis B virus (HBV), defined by presence of hepatitis B surface antigen (HepBsAg) and hepatitis B core antibody (HepBcAb);

   - Hepatitis C virus (HCV), defined by presence of hepatitis C antibody (HCVAb), and HCV RNA (when reflexed based on a positive result for HCVAb);

- Human Immunodeficiency Virus (HIV) infection, defined as presence of HIV antibody;
- Known diagnosis of primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, or overlap syndrome;
- History of esophageal varices, ascites, or hepatic encephalopathy;
- Alcoholic liver disease;
- Wilson's disease, defined as ceruloplasmin level <LLN;
- Known diagnosis of hemochromatosis;
- α-1-antitrypsin (A1AT) deficiency, defined as A1AT level <LLN;
- Prior known drug-induced liver injury;
- Known or suspected hepatocellular carcinoma or other liver cancer;
- History of liver transplant, current placement on a liver transplant list, or current model of end-stage liver disease (MELD) score >12;
- Histological presence of cirrhosis on prior biopsy.

9. Subjects with **any** of the following medical conditions:
    - Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, ileal resection);
    - Diagnosis of type 1 diabetes mellitus;
    - Diagnosis of T2DM requiring pharmaceutical treatment(s);
        - NOTE: Subjects with diet-controlled T2DM who have an HbA1c ≤7.0 *are permitted* in this study.
    - Recent (ie, within the previous 6 months) history of congestive heart failure (New York Heart Association, NYHA, class III or IV) or unstable angina;
    - A history of myocardial infarction, stroke, **or** transient ischemic attack, in the previous 6 months of Screen 1;
    - Any malignancy not considered cured (except basal cell carcinoma and squamous cell carcinoma of the skin); a subject is considered cured if there has been no evidence of cancer recurrence in the previous 5 years;

- Active placement of medical devices in/on thoracic or abdominal cavities such as pacemakers, defibrillators.

10. Subjects with any anatomical or pathological abnormality that would either preclude or tend to confound the analysis of study data, including any clinically significant abnormal findings on MRI obtained at Screen 3, by the Sponsor-identified central imaging vendor, or subjects meeting criteria for contraindication for MRI, including the following:

    - History of severe claustrophobia impacting ability to perform MRI during the study despite mild sedation/treatment with an anxiolytic;

    - Subjects with metal implants, devices, paramagnetic objects contained within the body, and excessive **or** metal-containing tattoos;

    - Subjects unable to lie still within the environment of the MRI scanner or maintain a breath hold for the required period to acquire images despite mild sedation/treatment with an anxiolytic;

    - Subjects with abdominal girth greater than the bore size of the site's MRI system.

11. Subjects taking any prohibited concomitant medication(s) **or** those unwilling/unable to switch to permitted concomitant medication(s) [refer to Section 5.8];

12. Weight loss of ≥5% within 1 month prior to Screen 1;

13. Pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential; fertile male subjects who are unwilling or unable to use highly effective method(s) of contraception as outlined in this protocol (Section 4.4.4) for the duration of the study and for **at least 28 days** after the last dose of IP;

14. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to Screen 1 or during the study until the on-site follow-up visit;

15. History of sensitivity to heparin or heparin-induced thrombocytopenia ***only if*** heparin is used to flush intravenous catheters;

16. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of IP (whichever is longer);

17. Subjects with known prior participation in a trial involving PF-06865571 (ie, received at least 1 dose of IP);

18. Unwilling or unable to comply with the criteria in Section 4.4 of this protocol;

19. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study;

20. At Screen 1, other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or IPadministration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.3. Randomization Criteria

On Day 1, interactive response technology (IRT) will be used to assign each eligible subject a randomization number, with this number recorded on the electronic Case Report Form (CRF). A computer-generated randomization code using the method of random permuted blocks will be utilized to randomize subjects in 1:1:1 ratio (1 of 2 active dosing regimens of PF-06865571 or placebo) prior to the first dose of IP, provided subjects satisfy **all** of the eligibility criteria outlined in Section 4.1 and Section 4.4.2.

- An attempt will be made to equally balance the number of subjects assigned to receive PF-06865571 versus placebo within each stratum by utilizing a 2-tiered stratification scheme as follows. Subjects will be stratified at randomization (Day1) first by the MRI-PDFF liver fat measurement determined by the Sponsor-identified central imaging vendor of images obtained during Screen 3:

- Screening liver fat ≥6% and <10%;

- Screening liver fat ≥10%.

- Subjects will then be stratified by the presence or absence of T2DM.

4.4. Lifestyle Requirements

After confirmation of eligibility at Screen 3, subjects will be instructed to maintain the guidelines described below for the duration of participation in the study. The following guidelines are provided.

4.4.1. Meals and Dietary Restrictions

- ≥4-hour fast (except water) prior to:

  - Liver fat assessment at Screen 3 using MRI-PDFF acquisition.

- ≥8-hour *overnight fast* (except water) prior to:

  - **Any** blood collection for lipids;

- Liver fat assessment on Day -2 and Day 15 via FibroScan® or MRI-PDFF.
- As dosing occurs **with meal/snack**, restriction regarding water intake prior to or after dosing is not expected.
- Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices - see below) may be consumed with meals and the evening snack.
- Breakfast will be provided approximately 30 minutes prior to AM dosing at 0H and is expected to be completed approximately 10 minutes prior to AM dosing.
- Lunch will be provided approximately 4 hours after dosing at 0H.
- Dinner will be provided approximately 10 hours after dosing at 0H.
- A snack consisting of at least 400 kcals will be provided at approximately 12 hours after the morning dose.
- The snack will be provided approximately 20 minutes prior to dosing.
- Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of IP until collection of the final PK blood sample.
- While confined, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein.
- The daily caloric intake per subject should **not** exceed approximately 3,200 kcal.
- The nutritional macronutrient composition consumed by each subject should be maintained, as much as practically possible, during the inpatient stay – though adjustment may be necessary based on serial assessment of body weight – refer to Schedule of Activities – Table 1 and Table 2 as well as Section 7.1.4.

- In a given subject, meals and snacks provided on Days -2, -1, 1, 14, and 15 must be identical and subjects encouraged to complete consumption of each meal/snack, whenever possible;
  - Meals and snacks offered on other days may vary – both for types of foods as well as macronutrient content.

4.4.2. Alcohol, Caffeine, and Tobacco

- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample. Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Subjects will abstain from caffeine-containing products for 2 hours prior to ECG and vital sign measurements.
- Subjects will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

4.4.3. Activity

- Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

4.4.4. Contraception

All fertile male subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of IP. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects 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 subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the postvasectomy ejaculate.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of IP and continuing for at least 28 days after the last dose of IP.

4.5. 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 supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and IP identifiers, subject study 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 subject'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 subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, IP is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the IPs are PF-06865571 and matching placebo and will be administered as oral tablets.

5.1. Allocation to Treatment

The IRT system will be used to sequentially assign a unique 8-digit subject identification number to each subject who has signed the informed consent document (ICD). This identifying number will be retained throughout the duration of study participation.

Allocation of subjects to treatment groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a randomization number. The IRT system will provide a confirmation report containing the subject number and randomization number. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

A computer generated randomization schedule will be used to assign approximately 45 subjects in a randomization ratio of 1:1:1 of the 3 treatment groups described in Table 5. The randomization number will be recorded in the CRF. In accordance with the randomization number, the subject will receive the study regimen assigned to the corresponding randomization number.

Table 5. Study Treatment Regimens and Dispensing Schedule

Treatment Group	Treatment Regimen	Morning	Evening
A	Placebo Q12H	3 x Placebo tablets	3 x Placebo tablets
B	50 mg PF-06865571 Q12H	1 x 50 mg tablet PLUS 2 x Placebo tablets	1 x 50 mg tablet PLUS 2 x Placebo tablets
C	300 mg PF-06865571 Q12H	3 x 100 mg tablets	3 x 100 mg tablets

- In order to maintain the double-blind design 50 mg, 100 mg, and matching placebo tablets will be supplied in the same size and shape;

- All dosing regimens (A-C) will consist of 3 tablets (representing PF-06865571 or matching placebo) administered Q12H.

5.2. Breaking the Blind

The study will be subject- and investigator-blinded.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

This is an investigator- and subject-blind (Sponsor open) placebo-controlled study. Blood specimens will be obtained from all subjects for pharmacokinetic analysis to maintain the study blind at the investigator site. The investigator site(s) staff [*with the exception of* the site pharmacist(s) and pharmacy assistant(s)], **and** blinded study monitor(s), will be blinded to investigational product (PF-06865571 or placebo). Other specified Pfizer personnel, *including the separate unblinded monitor(s) assigned*, will be unblinded to subject treatments. **The blinded study monitor will remain blinded to treatment until all monitoring for the study has been completed**.

Specimens from subjects 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.

5.3. Subject Compliance

IP will be administered under the supervision of investigator site personnel. The oral cavity of each subject will be examined following dosing to ensure the IP was taken.

5.4. Investigational Product Supplies

5.4.1. Dosage Form and Packaging

IP will be supplied by the Sponsor as PF-06865571 50 mg and 100 mg, and matching placebo tablets for oral administration. The tablets will be supplied as white to off-white tablets packaged in bottles and labeled according to local regulatory requirements.

5.4.2. Preparation and Dispensing

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

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

5.5. Administration

Administration of blinded IP will occur under the conditions described in Section 4.4.1. Subjects will receive the first dose of IP at approximately 08:00 hours local time (plus or minus 2 hours). The second dose will be administered approximately 12 hours later. Investigator site personnel will administer IP with ambient temperature water to a total

volume of approximately 240 mL. Subjects will swallow the IP whole, and will not manipulate or chew the IP prior to swallowing.

5.6. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all IPs are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

IPs should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the SRSD (ie, IB for PF-06865571) will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of IP receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product-label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the IP must be quarantined and not used until Pfizer provides permission to use the IP. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the IP prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP supplies. All IPs will be accounted for using a drug accountability form/record.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused IP (eg, at the site). 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, and all destruction must be adequately documented.

5.8. Concomitant Treatments

Subjects in this study will be allowed to take certain concomitant medications to treat coexisting conditions such as hyperlipidemia and hypertension. All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. Attempts must be made **not** to alter the doses and regimens of chronic background medications after randomization and for the duration of participation in this study. Any changes made to background medications must be captured in the CRF. All subjects will be questioned about concomitant treatment at each study visit.

Treatments taken within 42 days before the first dose of IP on Day 1 will be documented as a prior treatment. Treatments taken after the first dose of IP will be documented as concomitant treatments.

5.8.1. Anti-Hypertensive Medications

Use of background antihypertensive agent(s) is permitted. Doses of antihypertensive agents should be stable for at least **8 weeks** prior to Screen 1.

5.8.2. Lipid-Modifying Medications

Subjects are permitted to be on stable doses of the following lipid-modifying agents, starting at ≥**8 weeks** prior to Screen 1 and until on-site Follow-up visit, including (but not limited to) the following:

- Statins such as atorvastatin, simvastatin, pitavastatin, pravastatin;
- ***Note:*** rosuvastatin and fluvastatin are **not** permitted as detailed below;
- Ezetimibe;
- Bile acid sequestrants such as cholestyramine, colestipol, colesevalam;
- Gemfibrozil and fenofibrate;
- Nicotinic acid/niacin.

The use of the following medications or classes of agents is **not** permitted within the timelines specified:

- Rosuvastatin or fluvastatin within **4 weeks** prior to Screen 1 and until on-site Follow-up visit;
- Monoclonal antibodies inhibiting [redacted] such as alirocumab and evolocumab, within **12 weeks** prior to Screen 1 or within 5 half-lives of dose administered (whichever is longer), and until on-site Follow-up visit.

5.8.3. Other Acceptable Concomitant Medications

Subjects on the following list of medications must be on stable doses (ie, at least **8** weeks prior to Screen 1) and for the duration of participation in the study through on-site Follow-up visit:

- Inhaled and topical corticosteroids;
- Thyroid replacement therapy;
- Postmenopausal hormone therapy;
- Non-steroidal anti-inflammatory medications (NSAIDs) such as ibuprofen, ketoprofen, naproxen, indomethacin, and meloxicam. Intermittent use of these medications is also permitted;
- Intermittent use of acetaminophen/paracetamol at doses ≤1 gram per day;
- Aspirin at doses ≤325 mg per day;
- Antidepressant medications such as tricyclic agents, selective serotonin reuptake inhibitors, and serotonin/norepinephrine reuptake inhibitors;
- Certain herbal supplements ***but only*** following consultation with Sponsor;
- Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

5.8.4. Prohibited Concomitant Medications

Subjects must abstain from using ***all*** anti-diabetic medications for **≥12 weeks** prior to Screen 1 and until on-site Follow-up visit, including the following:

- Biguanides, such as metformin;
- Sulfonylureas such as glyburide, acetohexamide, chlorpropamide, tolazamide, tolbutamine, glimepiride, glipizide;

- Dipeptidyl peptidase-4 (DPP-4i) inhibitors such as sitagliptin, saxagliptin, vildagliptin;
- α-glucosidase inhibitors such as acarbose and miglitol;
- TZDs such as pioglitazone and rosiglitazone;
- Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, pramlintide);
- Sodium-glucose co-transporter 2 inhibitors such as canagliflozin, dapagliflozin, empagliflozin.

Subjects must abstain from using the following medications for **≥4 weeks** prior to Screen 1 and until on-site Follow-up visit:

- Chronic use of systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone; and immunosuppressants such as tacrolimus;
- Pharmacological agents with approved indication for weight loss such as orlistat and sibutramine;
- Over-the-counter appetite-simulant or appetite-suppressant, as advertised;
- (Medical-grade) marijuana, regardless of medical indication.
- Specific classes of agents given that the current study is the first study in a patient population:
    - Coumadin-type anticoagulants *or* other anticoagulants (eg, dabigatran);
    - Anticonvulsants;
    - Antiarrhythmics, except for beta blockers or calcium channel blockers if used for the management of conditions other than arrhythmias.
- Medications historically associated with fatty liver are prohibited if used for **≥4 weeks of continuous use** in the previous 12 months prior to Screen 1, examples include:
    - Amiodarone, methotrexate, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, other known hepatotoxins;
    - Strong inducers and inhibitors of CYP3A enzyme (see Appendix 2);

- BCRP and P-gp substrates (eg, rosuvastatin and digoxin);
- Sensitive CYP2C9 substrates (eg, fluvastatin, diclofenac, celecoxib, torsemide).

5.9. Rescue Medication

There is no rescue therapy to reverse AEs observed with administration of IP; standard medical supportive care should be provided to manage the AEs.

6. STUDY PROCEDURES

A signed and dated ICD will be obtained from each subject at Screen 1 before performing any protocol-specific procedures. All requirements and procedures of the trial will be thoroughly reviewed with all subjects. The results of the clinical laboratory assessments and all screening procedures will be evaluated with respect to inclusion and exclusion criteria to determine the subject's eligibility. If a subject does not qualify for the trial, he or she will be considered a screen failure. **Adverse Event (AE) reporting, including Serious Adverse Event (SAE) reporting will begin from the time the ICD is signed at Screen 1.**

6.1. Proposed Chronology of Procedures

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, *where possible*.

- *12-lead ECG*: obtain prior to vital signs assessment, blood samples, and prior to dosing (refer to Section 7.1.6).
- *Vital Signs (BP and pulse rate)*: obtain after 12-lead ECG collection but prior to obtaining blood samples and prior to dosing (refer to Section 7.1.5).
- *Fasting blood samples*: after assessment of 12-lead ECG and vital signs but prior to dosing (refer to Section 7.1.1).
- *Serial blood samples for plasma PK, insulin,* CCI [redacted] as close as practically possible to the scheduled time (refer to Schedule of Activities).
  - If the post-dose blood collection nominal time coincides with the nominal time of a meal, these blood samples should be collected just ***prior to*** meal/snack.
- *Other pre-dose procedures*: should be obtained/performed as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.
- *Dosing*: must occur at the scheduled nominal time (refer to Section 5.5) and following pre-dose blood sample collection.

- ***If*** an intravenous catheter is placed for serial blood sample collections, ECGs and vital signs (pulse rate, BP) assessments should be either collected prior to the insertion of the catheter or sufficient rest period after catheter insertion introduced to minimize impact of catheter placement on these assessments.

6.2. Screening

Refer to the Schedule of Activities Table 1 for the study procedures to be completed at the Screening visits. **The 3 screening visits are to be performed sequentially**.

- At Screen 1, subjects will be consented and all screening procedures (except assessment of liver fat by MRI-PDFF) undertaken to determine eligibility – refer to Sections 4.1 and 4.2;

- **Only** after subjects are identified to be otherwise eligible, should they proceed with Screen 2 for another FibroScan® assessment as performed at Screen 1;

- **Following** confirmation of all eligibility at Screen 2, subjects should proceed to the Imaging center for the Screen 3 visit to undergo liver fat assessment via MRI-PDFF acquisition to assess whether they meet inclusion criterion #4, Section 4.1.

Subjects will be screened **within 42 days** prior to the first dose of the blinded IP to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in Section 12.3.

In ***rare*** cases, subjects may be re-screened; however, this is permitted ***only*** when, due to ***logistical constraints***, the maximum period between the Screen 1 and Day 1 of **42 days** is exceeded. In such cases, all screening procedures must be repeated and the subject assigned a new 8-digit SSID number. Subjects must be deemed to meet all the eligibility criteria including assessment of liver fat via MRI-PDFF at Screen 3, under the new 8-digit SSID.

To prepare for study participation, subjects will be instructed on the use of Lifestyle Requirements (Section 4.4) and Concomitant Treatments (Section 5.8).

6.3. Study Period

Refer to the Schedule of Activities for the study procedures to be completed.

CCI [redacted]

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

If the subject is unable or unwilling to remain in the CRU and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.4. Follow-up

In this study, there are 2 follow-ups, as listed below:

- **1st follow-up is an on-site visit** where the subjects will return to the CRU between 7 to 10 days following the last dose of IP.
- **2nd follow-up is a telephone contact** that will occur 28 to 35 days following the last dose of IP. If the PI deems it necessary, this contact may be a visit.
- Refer to the Schedule of Activities for the study procedures to be completed at each of the 2 follow-ups.

6.5. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also Section 8.1.3) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given investigator site. The early termination visit applies only to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject twice. After 2 attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early-withdrawal visit, every effort must be made to complete the following assessments:

- Conduct an inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Full physical examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit (refer to Section 7.1.3);

- Supine, single standard 12-lead ECG measurement (refer to Section 7.1.6);
- Single, supine BP and pulse rate measurements (refer to Section 7.1.5);
- Blood and urine specimens for clinical laboratory tests (refer to Section 7.1.1);
- Blood sample for PK analysis for PF-06865571 (refer to Section 7.2);

CCI [redacted]

- Blood for cystatin C (refer to Section 7.1.2);
- Blood for insulin (refer to Section 7.3.4).

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

If the subject withdraws from the study and also withdraws consent 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.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment 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 subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects 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 investigational product 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 subject 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.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up

portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

7. ASSESSMENTS

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 subject. 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.

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.

Refer to Section 6.1 for the recommended order of collection when multiple procedures are scheduled at the same timepoint.

7.1. Safety

7.1.1. Laboratory Tests

The following clinical laboratory tests will be performed at times defined in the Schedule of Activities. 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 concerns.

Table 6. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea Creatinine *Plasma* glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase GGT Total bile acids Uric acid Albumin Total protein Direct bilirubin[d] Indirect bilirubin[d] *Serum* cystatin C	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• FSH[b] • Urine drug test[c] • Serology: HIV, HepBsAg, HepBcAb, HCVAb (and if positive, reflex HCV RNA)[c] • A1AT[c] • HbA1c[c] • Ceruloplasmin[c] • PT/INR[c]
Additional Tests (Needed for Hy's Law)			
• AST, ALT (repeat) • Total bilirubin (repeat) • Albumin (repeat) • Alkaline phosphatase (repeat) • Direct bilirubin • Indirect bilirubin • Creatine kinase • GGT • PT/INR • Total bile acids • Acetaminophen drug and/or protein adduct levels			

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. At Screening only, in all females.
c. At Screening only.
d. Direct and indirect bilirubin measured only when total bilirubin is >ULN.
For a list of abbreviations, refer to Appendix 1.

- The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.

- Subjects may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for subjects to receive IP.

- Estimated glomerular filtration rate (eGFR) will be calculated using the modification of diet in renal disease (MDRD) equation.

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. CCI [redacted]

[redacted]

CCI [redacted] These data will not be included in the clinical study report (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.

7.1.2. Serum for Cystatin C

Blood samples (approximately 2.5 mL) to provide a sufficient quantity of serum for analysis of cystatin C will be collected into appropriately labeled tubes at pre-specified nominal time points outlined in the Schedule of Activities. GFR will be estimated from the cystatin C using the CKD-Epi-Cystatin C equation[18] provided below.

- For serum cystatin C (Scys) ≤0.8 mg/L:

  $$eGFR = 133 \times (Scys/0.8)^{-0.499} \times 0.996^{Age} [\times 0.932 \text{ if female}]$$

- For serum cystatin C (Scys) >0.8 mg/L:

  $$eGFR = 133 \times (Scys/0.8)^{-1.328} \times 0.996^{Age} [\times 0.932 \text{ if female}]$$

7.1.3. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

7.1.4. Body Weight

In this study, assessment of body weight will occur at the nominal time points specified in the Schedule of Activities per the following specifications –

- Weight will be recorded using a calibrated scale placed on a stable, flat surface;
- *During the inpatient stay*, the same scale will be used with the scale reporting weight in kilograms, and accuracy to the nearest 0.1 kg [ie, the device must be able to distinguish a difference between 68.4 kg and 68.3 kg];
- Measurement must be undertaken –
- At approximately the same time of the day, in the morning in the fasting state, at each nominal time point *while inpatient*;
- After the subject has been asked to void (ie, forced void);

- Under standard conditions (eg, subjects must wear light clothing with content of their pockets emptied or hospital gown **and not** be wearing shoes or bulky layers of clothing/jackets);

- With subjects remaining still while on the weighing scale.

7.1.4.1. Adjustment of Caloric Intake to Maintain Stable Body Weight

- Daily caloric intake, *while inpatient*, should be adjusted based on *each* serial assessment of body weight ***after*** Day 1 – refer to Section 4.4.1;

- The initial caloric intake/menu assigned to each subject will be based on the Harris Benedict formula (sedentary lifestyle; to be provided to the site prior to study start) using the subject's body weight measured at screening;

- Caloric intake should be adjusted, on the days when body weight is assessed, to ensure that the subjects do not gain or lose body weight – defined as no more than ±1.0 kg change in body weight on any day post Day 1 **compared to the body weight at Screen 1;**

- NOTE: on **selected** days when meals and snacks offered are to be identical (ie, Days -2, -1, 1, 14, and 15), while body weight measurements may occur on some of these days, adjustment to caloric content on these **selected** days must **not** occur.

7.1.5. Blood Pressure and Pulse Rate

BP and pulse rate will be measured at times specified in the Schedule of Activities section of this protocol. 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.

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

7.1.6. Electrocardiogram

In this study, 12-lead ECGs will be collected at the nominal time points specified in the Schedule of Activities per the following specifications:

- All scheduled 12-lead ECGs should be performed after the subject has rested quietly for ≥10 minutes in a supine position;

- Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected prior to the first dose on Day 1 will serve as each subject's baseline value.

- If the average of QTcF values from the triplicate measurements remains above the threshold value (ie, is ≥45 msec from the baseline, or is ≥500 msec), 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 QTcF values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner, at the discretion of the investigator), or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner, at the discretion of the investigator).

- Further ECG monitoring will occur if a) a post-dose QTcF interval is increased by ≥30 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 remains 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.

In some cases, it may be appropriate to repeat abnormal 12-lead ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are 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 physician's interpretation determines that the QTcF values are in the acceptable range.

ECG data will be submitted to a central laboratory for overread measurement of ECG intervals and overall interpretation. The central ECG laboratory will be blinded to treatment allocation. The final ECG report from the central laboratory should be maintained in the subject's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the Baseline/Day 1 ECG may potentially be adverse events (AEs) (Section 8.2) and evaluated further, as clinically warranted.

7.2. Pharmacokinetics

7.2.1. Plasma for Analysis of PF-06865571

Blood samples (approximately 4 mL) to provide a sufficient amount of plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) at times specified in the Schedule of Activities section of the protocol.

PK sampling time points in this study may be adjusted to adequately assess the plasma PK profile based on emerging data. The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 2 hours of the nominal time from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (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. 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 IP, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, CCI [redacted] These data will not be included in the CSR.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

7.5. Imaging Assessments

7.5.1. Assessment of Liver Fat and Stiffness Using FibroScan®

In this study, estimation of liver fat and stiffness using FibroScan® will occur at scheduled visits outlined in the Schedule of Activities. Each acquisition will take approximately 10 minutes and requires the subject to be in a supine position with the right arm placed flat above the head. Acquisition results do *not* need independent over-read, but steps to ensure the acquisition was complete and accurate are required, as per training to be provided by EchoSens (vendor supporting the device) at the start of the study. As much as practically possible, attempts will be made to ensure each individual subjects' assessment is performed by the same operator. All FibroScan® operators will be trained and certified by EchoSens, and must be a sonographer or comparable.

Complete details regarding acquisitions using FibroScan® to assess liver fat by CAP™ and LSM will be provided by EchoSens before initiation of this study. All images acquired must be saved by the study site until the conclusion of 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 subject's source documents.

The FibroScan® is performed on the right lobe of the liver through intercostal spaces via a transducer probe that delivers a painless, mechanical impulse to the liver and measures the resulting shear wave. The LSM is directly proportional to the velocity of the shear wave. Simultaneously, the CAP™ measures the ultrasonic attenuation coefficient in the forward and return path of the radio-frequency pulse through the liver. The device calculates the median LSM and liver fat values by CAP™ after a total of 10 valid, serial measurements are acquired per assessment.

CCI [redacted]

7.5.2. Assessment of Liver Fat Using MRI-PDFF Acquisition and Analysis

At scheduled visits (refer to the Schedule of Activities), liver fat will be assessed via MRI, using the PDFF acquisition protocol.

Across the study sites selected for this study, the Sponsor-identified central imaging vendor will train the staff at the Imaging facility on the MRI-PDFF acquisition protocol, on real time review of image quality and readability of the acquired images, and on transfer (preferably electronically) of the images to the Sponsor-identified central imaging vendor for analysis and quantification of liver fat. **Only the staff members at the Imaging facility who are trained by the Sponsor-identified central imaging vendor are permitted to acquire images in the subjects who consent for this study,** however in rare/limited situations, exceptions may be granted with written approval of the Sponsor. Complete details on the MRI-PDFF acquisition protocol, determination of quality of images, and transmission of data

to Sponsor-identified central imaging vendor will be provided in an Imaging Manual offered to the study sites prior to the start of the study.

As much as practically possible, analysis of the MRI-PDFF images acquired from baseline (Day -2) to end of treatment will be undertaken by a single colleague at the Sponsor-identified central imaging vendor who will be blinded to individual subject's clinical data, as well as randomization and stratification assignment.

The baseline (Day -2) assessment for MRI-PDFF should be at approximately the same clock time (ie, within a practical window (±2 hours) relative to clock time of the screening visit). All post-dose assessments for MRI-PDFF should occur within a practical window (±2 hours) relative to clock time of the baseline assessment.

7.5.3. Analysis of MRI-PDFF Images Including Determination of Eligibility

A subject's eligibility for this study based on liver fat as assessed via MRI-PDFF at Screen 3 will be made by the Sponsor-identified central imaging vendor, only. The individual subject's liver fat will not be communicated to the study site, only the stratum to which the subject is assigned. In the case of the MRI at Screen 3, study sites will only be informed whether a subject meets eligibility criteria or if the screening MRI should be repeated once, as determined by the Sponsor-identified central imaging vendor. For all subsequently scheduled MRI-PDFF assessments, study sites will only be informed whether the images are deemed evaluable (or not). Of note, subjects with non-evaluable baseline images (as determined by the Sponsor-identified central imaging vendor) may be withdrawn prior to or after randomization, at the discretion of the Sponsor.

7.5.4. Management of Incidental Findings

An incidental finding is one unknown to the subject 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 a Sponsor-identified central imaging vendor. The purpose of this review is to evaluate images for the amount of fat in the liver. Central image review is not a complete medical review of the subject. 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 principal investigator. 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-patient relationship. The principal investigator will be responsible for reporting any AEs identified from incidental findings as described in the ADVERSE EVENT 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 study site protocols.

7.5.5. Post-hoc Analyses

[redacted] Any such analyses will not be included in the CSR; but a separate supplemental report will be written to capture this work, if undertaken.

7.6. Potential Cases of Acute Kidney Injury

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

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

If the second (repeat) result is still increased by ≥0.3 mg/dL (or ≥26.5 μmol/L) relative to the subject's own baseline, assessment of eGFR using serum cystatin C should be performed. Based on these measurements, eGFR using SCr and serum cystatin C will be determined and reviewed, preferably within 72 hours, and not later than 96 hours from the confirmed (repeat) elevated SCr result.

If an individual subject demonstrates CONCOMITANT SCr-based AND serum cystatin C-based eGFR decline of ≥30% compared to the subject's baseline eGFR, then the subject should not be further dosed and adequate, immediate, supportive measures and treatment as clinically indicated. Referral to a nephrologist (preferably within 24 hours) is also recommended. If the subject cannot be seen by a nephrologist within 24 hours (as described above), then the subject may be sent to a local emergency room for evaluation and treatment as clinically indicated. Results should be repeated weekly or as indicated until the renal parameters are deemed to be stable by the nephrologist and/or PI.

Subjects 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. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, 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, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr.

7.7. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 390 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;

- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result 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; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

  Or that is considered to be:

  - An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;

- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (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 lab 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 subject's individual baseline values and underlying conditions. Subjects 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:

- Subjects 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 subjects 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 subject 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, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. 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 (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) 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.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.2.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, 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. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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 includes 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 investigational product.

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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. 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's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject 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.

8.4.3. Medication Errors

Other exposures to the investigational product 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

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

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 immediately.

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 non-serious, are recorded on an 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**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a 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. Sample Size Determination

Approximately 15 subjects per arm are planned in this study for a total of approximately 45 subjects. Assuming an approximate 5% premature withdrawal rate, this will ensure a minimum of 42 subjects complete the study. With this sample size the power to detect a 25% mean reduction in MRI-PDFF relative to placebo is at least 79% using a 1-sided Type I error rate of 0.1. This calculation assumes the pooled SD of the log-relative change of 0.36 (based on an internal study).

9.2. Efficacy Analysis

The primary analysis population for all efficacy analyses will include all randomized subjects who received at least 1 dose of study medication (Full Analysis set).

9.2.1. Analysis of the Primary Endpoint

The primary endpoint will be the relative change from baseline at Day 15 in whole liver PDFF. Baseline will be the closest measurement prior to first dose on Day 1. An analysis of covariance (ANCOVA) will be performed on log-transformed relative change with treatment and baseline diabetic status as factors, log-transformed baseline whole liver PDFF value as a covariate. Estimates of the mean relative changes between each active dose and placebo at Day 15, and the corresponding 80% confidence interval (CI) will be obtained from the model. Each comparison of PF-06865571 dose with the placebo will be performed at a Type I error rate of 10% (1-sided). No adjustment for multiple comparisons will be made. If the model does not fit the data group medians and their differences from the placebo median will be presented. The details will be provided in the SAP.

Descriptive summaries of the observed values and percent change from baseline in whole liver PDFF for each treatment group will also be produced.

CCI [redacted]

9.3. Pharmacokinetic Analysis

The PK concentration population will be defined as all randomized subjects who received at least 1 dose of PF-06865571 and in whom at least 1 plasma PK concentration value is reported. The PK parameter analysis population will be defined as all randomized subjects who received at least 1 dose of PF-06865571 and who have at least 1 of the PK parameters of interest calculated. PK samples from placebo samples will not be routinely analyzed.

9.3.1. Derivation of Pharmacokinetic Parameters

The PK parameters for PF-06865571 will be derived from the concentration-time profiles as data permit. The various PK parameters to be assessed in this study, their definition and method of determination are outlined in Table 7. Actual PK sampling times will be used in the derivation of PK parameters.

Table 7. Definition of Steady State (Day 14) Plasma PK Parameters for PF-06865571

Parameter	Definition	Method of Determination
AUC_{tau}	Area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval	Linear/Log trapezoidal method
C_{max}	Maximum plasma concentration during the dosing interval	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
CL/F	Apparent clearance	$Dose/AUC_{tau}$
C_{min}	Minimum plasma concentration during the dosing interval	Observed directly from data
PTR	Peak-to-trough ratio	C_{max}/C_{min}

The above listed PK parameters will be summarized descriptively by dose. Relationships between PF-06865571 PK and safety and/or efficacy endpoints may also be explored, but may not be included in the final CSR.

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

9.6. Safety Analysis

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. 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 physical examination information 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 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.

9.6.1. Electrocardiogram Analysis

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

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

Safety QTcF Assessment

	Borderline (msec)	Prolonged (msec)
Absolute value	≥450 - <480	≥480
Absolute change	30-<60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be listed.

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 subject factors (covariates) on the relationship will be examined. The analysis, if conducted, may not be reported.

9.7. Interim Analysis

Interim analyses may be performed to assess efficacy and/or safety after at least 50% of the planned subjects, ie, approximately 21 subjects, complete the study. Interim analysis results may be used for internal business decisions regarding future study planning, stopping for futility, conducting a sample size reestimation, or adapting the study after the interim analysis. Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an internal review committee (IRC) charter. In addition, the analysis details will be documented and approved in an interim analysis SAP or final SAP.

9.8. Data Monitoring Committee

This study will not use a data monitoring committee (DMC). This study will potentially use an IRC comprised of Pfizer employees (or designees) who are not directly involved in the day-to-day conduct of the study. If an IRC is used then an IRC charter will be developed to govern the details of the interim analysis and IRC operations.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer investigator sites, 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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRFis required and should be completed for each included subject. The completed original CRFsare the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFsand any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFsmust be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFsare true. Any corrections to entries made in the CRFsor source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFsmust match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRFand for which the CRFwill stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFsand hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject’s numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects’ personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. 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 investigational product, 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in the United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06865571 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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 US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual patients have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Yen CL, Stone SJ, Koliwad S, et al. Thematic review series: glycerolipids. DGAT enzymes and triacylglycerol biosynthesis. J Lipid Res 2008;49(11):2283-301.

2. Buhman KK, Smith SJ, Stone SJ, et al. DGAT1 is not essential for intestinal triacylglycerol absorption or chylomicron synthesis. J Biol Chem 2002;277(28):25474-9.

3. Cases S, Stone SJ, Zhou P, et al. Cloning of DGAT2, a second mammalian diacylglycerol acyltransferase, and related family members. J Biol Chem 2001;276(42):38870-6.

4. Choi CS, Savage DB. Suppression of diacylglycerol acyltransferase-2 (DGAT2), but not DGAT1, with antisense oligonucleotides reverses diet-induced hepatic steatosis and insulin resistance. J Biol Chem 2007;282(31):22678-88.

5. Yu XX, Murray SF, Pandey SK, et al. Antisense oligonucleotide reduction of DGAT2 expression improves hepatic steatosis and hyperlipidemia in obese mice. Hepatology 2005;42(2):362-71.

6. Liu Y, Millar JS, Cromley DA, et al. Knockdown of acyl-CoA:diacylglycerol acyltransferase 2 with antisense oligonucleotide reduces VLDL TG and ApoB secretion in mice. Biochim Biophys Acta 2008;1781(3):97-104.

7. Fon Tacer K, Rozman D. Nonalcoholic fatty liver disease: focus on lipoprotein and lipid deregulation. J Lipids 2011;1-14.

8. Marchesini MB, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes, 2001;50(8):1844-50.

9. Hass JT, Francque S, Staels B. Pathophysiology and mechanisms of nonalcoholic fatty liver disease. Ann Rev Physiol 2016;78:181-205.

10. Sanyal AJ, Friedman SL, McCullough AJ, et al. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations from an American Association for the Study of Liver Diseases-U.S. Food and Drug Administration Joint Workshop. Hepatology 2015;61(4):1392-405.

11. Cohen JC, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. Science 2011;332(6037):1519-23.

12. Sanders FWB, Griffin JL. De novo lipogenesis in the liver in health and disease: more than just a shunting yard for glucose. Biol Rev 2016;91:452-68.

13. Lambert JE, Ramos-Roman MA. Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease. Gastroenterology 2014;146 (3):726-35.

14. Noureddin M, Lam J, Peterson MR, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology 2013;58:1930-40.

15. Le TA, Chen J, Chanqchien C, et al. Effect of colesevelam on liver fat quantified by magnetic resonance in nonalcoholic steatohepatitis: a randomized controlled trial. Hepatology 2012;56:922-32.

16. Loomba R, Sirlin CB, Ang B, et al. Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART Trial). Hepatology 2015;61:1239-50.

17. Motohashi H, Inui K. Organic cation transporter OCTs (SLC22) and MATEs (SLC47) in human kidney. AAPS J 2013; 15(2):581-8.

18. Inker LA, Schmid CH, Tighiouart H, et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. N Engl J Med 2012; 367:20-9.

19. Pischon T, Girman CJ, Sacks FM, et al. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 2005; 112(22): 3375-83.

20. Rhainds D, Arsenault BJ, Tardif JC. PCSK9 inhibition and LDL cholesterol lowering: the biology of an attractive therapeutic target and critical review of the latest clinical trials. Clin Lipidol 2012:7(6):621-40.

Appendix 1. Abbreviations

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

Abbreviation	Term
A1AT	α-1-antitrypsin
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
CCI [redacted]	[redacted]
BA	bioavailability
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
BE	bioequivalence
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CAP	controlled attenuation parameter
CFB	change from baseline
CI	confidence interval
CK	creatine kinase
CLr	renal clearance
C_{max}	maximum observed concentration
C_{min}	minimum concentration
CO2	carbon dioxide (bicarbonate)
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DAG	diacylglycerol
DDI	drug-drug interaction
DGAT	diacylglycerol acyltransferase
DILI	drug-induced liver injury
DMC	data monitoring committee

Abbreviation	Term
CCI [redacted]	[redacted]
DNL	de novo lipogenesis
DPP-4	dipeptidyl peptidase-4
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
EDTA	edetic acid (ethylenediaminetetraacetic acid)
eGFR	estimated glomerular filtration rate
EU	European Union
EudraCT	European Clinical Trials Database
FA	fatty acids
FFA	free fatty acids
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
H	hour(s)
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
CCI [redacted]	[redacted]
HIV	human immunodeficiency virus
CCI [redacted]	[redacted]
IB	investigator's brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IWR	interactive Web-based response

Abbreviation	Term
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
kPa	kilopascal
LDL-C	low density lipoprotein cholesterol
LFT	liver function test
LLN	lower limit of normal
LSLV	last subject last visit
CCI	[redacted]
MATE	multi-drug and toxin extrusion protein
mBCRP	mouse breast cancer resistant protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR1	multi-drug resistance protein 1
MDRD	modification of diet in renal disease equation
MELD	model of end-stage liver disease
MGAT	monoacylglycerol acyltransferase
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
N/A	not applicable
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NOAEL	no observed adverse effect level
NSAIDs	non-steroidal anti-inflammatory medications
NYHA	New York Heart Association
OAT	organic anion transporter
OATP	organic anion transporter polypeptide
OCT	organic cation transporter
PBPK	physiologically based pharmacokinetic
PCD	primary completion date
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PDFF	proton density fat fraction
P-gp	P-glycoprotein
pH	potential of hydrogen
PI	principal investigator
PIB	powder in bottle
PK	pharmacokinetic(s)
PT	prothrombin time
PTR	peak to trough ratio
Q8H	every 8 hours
Q12H	every 12 hours

Abbreviation	Term
QTc	corrected QT interval
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SOP	standard operating procedure
SRSD	single reference safety document
$t_{1/2}$	Half-life
TBili	total bilirubin
T2DM	type 2 diabetes mellitus
TG	triglycerides
THC	tetrahydrocannabinol
T_{max}	time to reach maximum concentration
UDP	uridine diphosphate
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States
CCI	[redacted]
VLDL	very low density lipoprotein
WBC	white blood cell

Appendix 2. Strong CYP3A Inhibitors and Inducers*

CYP 3A Inhibitors	CYP 3A Inducers
HIV antivirals	**HIV antivirals**
Indinavir	Nevirapine
Nelfinavir	**Miscellaneous**
Ritonavir	Barbiturates
Saquinavir	Carbamazepine
Boceprevir	Glucocorticoids (systemic)
Lopinavir/ritonavir	Oxcarbazepine
Amprenavir	Phenobarbital
Atazanavir	Phenytoin
Telaprevir	Rifabutin
Darunavir/ritonavir	Rifampin
Fosamprenavir	St. John's wort[3]
Tiprinavir/ritonavir	Troglitazone
Antibiotics	Nafcillin
Clarithromycin	Avasimibe[4]
Troleandomycin	Enzalutamide
Telithromycin	Mitotane
Anti-infectives	
Itraconazole	
Ketoconazole	
Posaconazole	
Voriconazole	
Miscellaneous	
Nefazodone	
Grapefruit juice[1]	
Conivaptan	
Mibefradil[2]	
Idelalisib	

1. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
2. Withdrawn from the United States market.
3. The effect of St. John's wort varies widely and is preparation-dependent.
4. Not a marketed drug.

* This list is not considered as exhaustive. Any questions regarding use of CYP3A inhibitors and inducers should be directed to the Sponsor study team.

Reference: U.S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm