A PHASE 2A, RANDOMIZED, DOUBLE BLIND (SPONSOR-OPEN), PLACEBO CONTROLLED, PARALLEL GROUP STUDY TO ASSESS THE PHARMACODYNAMICS, SAFETY AND TOLERABILITY OF PF-05221304 AND PF-06865571 CO-ADMINISTERED FOR 6 WEEKS IN ADULTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Investigational Product Number:	PF-05221304 and PF-06865571
Investigational Product Name:	Not Applicable
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
Protocol Number:	C3711001
Phase:	2a

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	02 October 2018	This amendment is making the following substantial changes as requested by the United States Food and Drug Administration (US FDA) as part of their review of the Original protocol submitted on 15 August 2018. 1. In response to agency's request to remove the term "metabolic syndrome" from Inclusion Criterion #5 (Section 4.1), the text was modified to reflect that the ≥2 out of 5 criteria listed should be met; the criteria being "commonly associated" with metabolic syndrome instead of original text, which reflected that 5 criteria may be indicative of metabolic syndrome. 2. In response to agency's request to add trial stopping criteria, an additional sub-section was added in Study Design ie, Section 3.3: "Considerations for Pausing or Stopping Treatment Arm or Trial Based on Observed Safety". The sub-section outlines the rules for pausing or stopping a treatment arm or Trial. Modifications in text were also made in related Section 9.8. 3. In response to agency's request to establish baseline values for liver enzymes by at least two samples obtained at least 4 weeks apart to account for disease related changes in liver enzymes and bilirubin, text was added to the Exclusion Criterion #2 (Section 4.2) to clarify that subjects meeting the exclusion criterion for liver enzymes and bilirubin laboratory values in either Visit 1 **or Visit 4** will be excluded from the study. The study design Figure 1: C3711001 Study Design was revised to reflect that the time duration between Screen 1 (Visit 1) and Visit 4 (start of Run-In) is expected to be at least 4 weeks, but not to exceed 6 weeks, thereby, fulfilling a minimum 4 week time period requirement between 2 visits. Schedule of Activities and text in Section 3.1 and Section 6.1

		was modified to reflect changes to Figure schematic. In addition to the FDA requested changes, following revisions have been made to the protocol in this Amendment: 4. Schedule of Activities: In Table 1, text in column header "Treatment Phase" was modified to include the phrase " ….unless otherwise noted" to accommodate post-dose PK collections which will be conducted 2 hours post dosing. 5. Schedule of Activities: For Visit 10, instead of allowed ±2 days from Day 42 visit, the allowable window has been changed to '42(-3)' ie, subjects are allowed to make Visit 10 up to 3 days in advance of Day 42 visit, but not beyond Day 42. This change was made to ensure to limit potential medication errors of dosing beyond 42 days specified by the protocol. Additional footnote "b" was added to clarify the visit window. 6. Schedule of Activities, Section 5.4.2, and Section 5.5: Text was added in foot note "k" of Table 1, in Section 5.4.2 and Section 5.5 to clarify that on Visit 10, there will not be any evening dose. 7. Section 1.4.2 Text was modified to clarify the language regarding potential effect of PF-06865571 in inhibiting OCT2/MATE. 8. Section 1.5.1: A typographical error was made in the dose rationale text. The error was rectified as below: "The anticipated exposures of PF-05221304 at 15 mg BID in this study are 122-fold and 29-fold

		~~higher~~ lower (C_{max} and AUC_{24}, respectively) than the NOAEL (30 mg/kg (QD) PF-05221304 + 300 mg/kg (BID) PF-0686557) in the 6-week combination toxicology study in monkeys. Similarly, the anticipated exposures of PF-06865571 at 300 mg BID in this study are 3.7 and 6.2-fold ~~higher~~ lower than the 6-week monkey NOAEL." CCI [redacted] [redacted] 10. Section 1.5.2: Under heading 'Clinical Experience with Combination of PF-05221304 and PF-06865571', a brief summary was added regarding trends of fasting triglyceride levels observed in C3711002 Cohort 2. This summary was unintentionally excluded in the original version. 11. Section 4.1, Inclusion Criterion #6: Divided text from a single inclusion criterion (#6 in Original Protocol) into 2 individual inclusion criteria. Instead of Inclusion Criterion #6 in the Original protocol which stated that "At Screen 1 and Screen 2 ***both*** …." Inclusion Criterion #6 in this Amendment states "At Screen 1…". In addition, Criterion #7 has been added which states "At Screen 2…". This change was made to properly capture protocol deviations associated with each criterion in the eCRFs (electronic case report forms). 12. Section 4.2, Exclusion criterion #3: Language modified to clarify that subject has to be negative for urine drug test at Screen 1 (Visit 1), start of Run-in (Visit 4) and at Baseline

		(Visit 6) visit in order to enroll and remain in the study, not just Screen 1 (Visit 1) as implied in the Original Protocol. 13. Section 6.4.4 and Footnote "g" in Schedule of Activities Added text to clarify that if MRI-PDFF assessment for Visit 10 is completed on the day of the site visit for Visit 10, subjects should refrain from taking IP until blood draw for laboratory assessments is completed.
Original protocol	09 August 2018	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

SCHEDULE OF ACTIVITIES

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

Table 1. Schedule of Activities

Visit Identifier	**Screen 1**	**Screen 2**	**Screen 3**	**Run-In**	**Baseline**[a]	**Treatment Phase** [all procedures *before* morning dose of blinded IP, unless otherwise noted]					**Follow-up**		**Early Termination (ET)**
Week Relative to Dosing on Day 1	**Visit 1 to Visit 4 should be ≥4 and ≤6 weeks**			**-2**	**-1**	**0**	**1**	**2**	**4**	**6**	**7-14 days post last dose**	**28-35 days post last dose**[c]	
Days Relative to Dosing on Day 1				**-14±2**	**-4±2**	**1**	**5±1**	**14±2**	**28±2**	**42(-3)**[b]			
Visit to Site or Imaging Facility	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**--**	
Informed consent & demography	X												
Medical history	X												
Medication history (update)[d]	X			X		X	X	X	X	X	X	X	X
CCI FibroScan®)[e]	X	X				X		X	X	X			
Liver fat (via MRI-PDFF)[e,f]			X		X					X[g]			X[h]
Physical examination (PE)[i]	X			X		X				X	X		X
Body weight (+ hula-hoop test at Screen 1 only)	X			X		X				X	X		X
Single, supine 12-lead ECG	X			X		X	X	X	X	X	X		X
Single, seated vitals assessment (BP & pulse rate)	X			X		X	X	X	X	X	X		X
Serious and non-serious adverse event (AE) monitoring	X	→	→	→	→	→	→	→	→	→	→	X	X
Randomization in trial (via IRT)						X							
Dispense Investigational Product (IP) (via IRT)[j]				X		X		X	X				
Administration of IP[k]				X	→	X	X	X	X	X			
Compliance via pill count of returned IP						X	X	X	X	X			X
Confirm contraceptive method	X			X		X	X	X	X	X	X		
Instructions on Dosing of IP				X		X	X	X	X				
Counseling on diet/exercise guidelines				X		X		X	X	X	X		
Blood Collections after ≥8-hour, preferably 10-hour fast; refer to Table 7 for additional details													
Clinical laboratory tests	X			X		X	X	X	X	X	X		X
Cystatin C[l]	X			X		X	X	X	X	X	X		X

Visit Identifier	**Screen 1**	**Screen 2**	**Screen 3**	**Run-In**	**Baseline**[a]	**Treatment Phase** [all procedures *before* morning dose of blinded IP, unless otherwise noted]					**Follow-up**		**Early Termination (ET)**
Week Relative to Dosing on Day 1	**Visit 1 to Visit 4 should be ≥4 and ≤6 weeks**			**-2**	**-1**	**0**	**1**	**2**	**4**	**6**	**7-14 days post last dose**	**28-35 days post last dose**[c]	
Days Relative to Dosing on Day 1				**-14±2**	**-4±2**	**1**	**5±1**	**14±2**	**28±2**	**42(-3)**[b]			
Visit to Site or Imaging Facility	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**--**	
Serology (HepBsAg, HepBcAb, HCVAb, HCV RNA, HIV), Serum FSH (females only)	X												
Ceruloplasmin, Coagulation (aPTT, PT, PT/INR), α1-antitrypsin (A1AT)	X												
[redacted] CCI													
Fasting Lipid Panel	X			X		X	X	X	X	X	X		X
CCI [redacted]													
Apolipoproteins (A1, B100 and C3)						X				X			
CCI [redacted]													
Plasma PCSK9						X				X			
OATP Pharmacogenomics blood sample[o]						X							
Banked bio-specimen: Prep D1.5[o]						X							
Banked bio-specimen: Prep B1.5 and B2.5						X				X			
Urine Collections													
Urine drug test[p]	X			X		X							
Urinalysis (and microscopy, as appropriate)	X			X		X	X	X	X	X	X		X

Abbreviations: →= ongoing/continuous event; A1AT = α1-antitrypsin; AE = Adverse Event; aPTT = activated Partial Thromboplastin Time; BP = Blood Pressure; CCI [redacted] ECG = electrocardiogram; ET = Early Termination; FSH = Follicle Stimulating Hormone; CCI [redacted] HCVAb = Hepatitis C Virus Antibody; HCV RNA = Hepatitis C Virus Ribonucleic Acid; HepBcAb = Hepatitis B Core Antibody; HepBsAg = Hepatitis B Surface Antigen; HIV = Human Immunodeficiency Virus; CCI [redacted]; IP = Investigational Product; IRT = Interactive Response Technology; MRI-PDFF = Magnetic Resonance Imaging – Proton Density Fat Fraction; OATP = Organic Anion Transporter Polypeptide; PCSK9 = Proprotein Convertase Subtilisin/kexin type 9; PE = Physical Examination; CCI [redacted]; CCI [redacted] PT = Prothrombin Time; PT/INR = Prothrombin Time/International Normalized Ratio

a. baseline for liver fat assessments by MRI-PDFF is Day -4±2; baseline for all other assessments is Day 1, prior to first dose.

b. The Day 42 visit can occur up to 3 days prior ie, Day 39 to Day 42, but no later than Day 42.

c. To occur via telephone contact and must occur within 28-35 days from administration of the final dose of double-blind IP; this contact can be considered as on-site in order to permit follow-up of open AEs and/or abnormal laboratory tests from prior visit(s), as needed.

d. Update at post-screening visits.

e. Assessment to be performed following ≥4-hr fast, at site (as part of site visit) or separate visit(s) to Imaging facility; attempts to be made to perform baseline visit for each assessment (Visit 6 for FibroScan® and Visit 5 for MRI-PDFF) within ±2-hr window of initial screen time (Visit 1 for FibroScan® and Visit 3 for MRI-PDFF). Post-randomization assessments should be within ±2-hr window of baseline visit time (Visit 6 for FibroScan® and Visit 5 for MRI-PDFF).

f. A single repeat assessment is permitted at screening as determined by sponsor-identified central imaging vendor; at baseline (Visit 5) and at Visit 10, single repeat is permitted only after consultation with the Sponsor.

g. MRI-PDFF assessment to be performed within approximately 24 hours prior to Visit 10, or on the same day as Visit 10. If subjects perform MRI-PDFF in the morning of same day as Visit 10 visit, they should wait for blood collections before administration of morning dose at the site. Subjects will not take evening dose on Day 42.

h. MRI-PDFF will be obtained only for those subjects who receive at least 4 weeks of double-blind IP ie for subjects who drop out after Visit 9.

i. Includes arm and waist circumference, and height at Visit 1 only; targeted PE at Visit 4, Visit 6, Visit 10, Visit 11 and Early Termination; limited PE for follow-up on open AEs/abnormal tests, at investigator discretion.

j. Visit 4 and Visit 5 reflect single-blind placebo regimen; from Visit 6 onwards, reflects double-blind randomized regimen.

k. Administration of single or double-blind IP is twice daily; administration of witnessed dosing at site is on the mornings of Visit 4 for single-blind IP and on the mornings of Visit 6, Visit 7, Visit 8, Visit 9, and Visit 10 for double-blind IP, with meal. On these visits, evening dose to be administered as outpatient, with evening meal, except for Visit 10 for which, subjects will not take evening dose.

l. Review of Cystatin C results not required for dosing or discharge.

CCI [redacted]

o. If not collected on the designated collection day, collect at the next available time point when bio-specimens are being collected in conjunction with a subject visit.

p. A dipstick, provided by Sponsor-identified central lab, will be used.

1. INTRODUCTION

The dual acetyl-CoA (coenzyme A) carboxylase 1 and 2 (ACC1/2) inhibitor PF-05221304 and the diacylglycerol acyltransferase 2 (DGAT2) inhibitor PF-06865571 are each currently in clinical development as monotherapy agents for the treatment of non-alcoholic steatohepatitis (NASH) with liver fibrosis. Nevertheless, as exemplified by other metabolic disorders (eg, type 2 diabetes, dyslipidemias, etc), it is possible that a single drug may be insufficient to successfully treat NASH and therefore, combination therapy is being considered as an early intervention strategy. Inhibition of ACC1/2 by PF-05221304 and inhibition of DGAT2 by PF-06865571 are anticipated to modulate lipid metabolism in distinct and complementary ways, suggesting that co-administration of the two investigational agents may lead to greater efficacy than either agent administered alone.

PF-05221304 is a potent, selective, orally bioavailable, and reversible dual acetyl-CoA (coenzyme A) carboxylase 1 and 2 (ACC1/2) inhibitor (ACCi) designed to have asymmetric distribution to the liver, with ≥100 fold asymmetric hepatic distribution demonstrated in both rats and monkeys. ACC inhibition stimulates fatty acid oxidation, suppresses hepatic *de novo* lipogenesis (DNL), and reduces steatosis in animal models[1] and in humans.[2] As a result of its asymmetric distribution favoring the liver, PF-05221304 is expected to inhibit DNL and stimulate fatty acid oxidation in the liver to a greater extent than in peripheral tissues. In humans, administration of PF-05221304 has been shown to suppress hepatic DNL in a Phase 1 study in healthy adult subjects. This inhibition of hepatic DNL is postulated to result in a decrease and normalization of the excessive DNL observed in non-alcoholic fatty liver disease (NAFLD), and consequently reduce fat accumulation in the liver. Emerging data also suggest that suppression of DNL through reduction in ACC activity restrains the formation of the inflammatory interleukin-17 secreting T cells of the T helper 17 lineage (Th17) cells which in turn promotes the development of anti-inflammatory Foxp3(+) regulatory T (Treg) cells.[3] Based on these observations, it is hypothesized that ACC1/2 inhibition by PF-05221304 may lead concurrently to reductions in liver fat content and anti-inflammatory effects, thus mitigating two key pathophysiologic drivers of NAFLD.

PF-06865571 is an oral, small molecule diacylglycerol acyltransferase 2 (DGAT2) inhibitor that is postulated to decrease hepatic triglyceride (TG) synthesis and hepatic lipid burden in NAFLD and NASH. Diacylglycerol acyltransferases (DGATs) catalyze the terminal step in TG synthesis; specifically, the esterification of a fatty acid with diacylglycerol (DAG) resulting in the formation of TG.[4] In mammals, two 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.[5] DGAT2 is highly expressed in the liver and adipose tissue.[6] 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.[7,8] 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.[8,9]

The purpose of this study is to assess if the liver fat lowering effect of co-administration of PF-05221304 and PF-06865571 is greater than the effect of PF-05221304 or PF-06865571, when administered alone. The study will also assess the safety and tolerability of co-administration of PF-05221304 and PF-06865571 and effects on selected pharmacodynamics/exploratory parameters eg triglycerides, in subjects with NAFLD.

1.1. Mechanism of Action/Indication

PF-05221304 is a potent, selective, orally bioavailable, and reversible dual ACC1/2 small molecule inhibitor, designed to have asymmetric distribution to the liver. It is being developed for the treatment of NASH with fibrosis.

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

1.2. Background and Rationale

The World Health Organization lists NAFLD and NASH as the most important conditions contributing to the global health burden due to liver diseases, with NASH acknowledged as a potentially fatal condition leading to cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[10] NASH is a clinical and histological subset of NAFLD (defined as presence of ≥5% hepatic steatosis in the absence of other liver disease etiologies) that is associated with increased all-cause mortality, cirrhosis and end-stage liver disease, increased cardiovascular mortality, and increased incidence of both liver related and non-liver related cancers.[11] It is diagnosed clinically by liver biopsy demonstrating steatosis, inflammation, and cytological ballooning of liver hepatocytes, often with varying degrees of fibrosis. NASH progresses with increasing severity of fibrosis, with cirrhosis developing in a subset of patients[11] and a common complication of cirrhosis being HCC.[12]

In a recent meta-analysis, the global prevalence of NAFLD was estimated at 25%, with the prevalence of NASH in the subset with biopsy-proven NAFLD assessed at 59%.[13] The majority of the population with NAFLD has simple steatosis which has, in general, a benign clinical course. A proportion of patients with NAFLD progress to having hepatocellular ballooning and lobular inflammation – taking close to a decade to progress from 1 stage to the next and 30-40 years to develop cirrhosis; however, a smaller subset of patients progress very rapidly (within 10 years) to liver cirrhosis from NAFLD.[14] Patients with NASH may be asymptomatic or have non-specific symptoms such as fatigue, despite having significant disease on liver biopsy and associated risk for progression to cirrhosis and liver-related mortality. The 5-year (67%) and 10-year (38%) survival rates in patients with NASH is significantly different than in those with NAFLD.[10] The pooled liver-specific and overall mortality incidence rate estimates among those with NAFLD were calculated at 0.8 and 15.4, respectively, per 1,000 person-years. In contrast, amongst the population with NASH, the incidence rate estimates were 11.8 (liver-specific) and 25.6 (overall) mortality.[13]

Elevated rates of hepatic DNL have been reported to be a distinctive characteristic of NAFLD.[15] 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.

As described above, inhibition of ACC1/2 by PF-05221304 and inhibition of DGAT2 by PF-06865571 are anticipated to modulate lipid metabolism in distinct and complementary ways, suggesting that co-administration of both agents may provide greater efficacy than either agent alone.

1.3. Background Information for PF-05221304

1.3.1. Nonclinical Experience with PF-05221304

PF-05221304 has been orally administered once-daily for up to 16 weeks in toxicity studies conducted in rats and monkeys. In addition, PF-05221304 has been evaluated in genetic toxicity studies, central nervous system (CNS) and cardiovascular safety pharmacology studies, dose range-finding and definitive embryo-fetal development (EFD) studies in rats and rabbits, fertility and early embryonic study in rats, and *in vitro* and *in vivo* phototoxicity studies. The no observed adverse effect level (NOAEL) in the 16-week study in rats was 15 mg/kg/day (in males) and 5 mg/kg/day (in females). These doses were associated with total maximum plasma concentration (C_{max}) of 6300 ng/mL (247 ng/mL, unbound) and total area-under-the-curve over dosing interval of 24-hours (AUC_{24}) of 40,300 ng•h/mL (1580 ng•h/mL, unbound) and total C_{max} of 1250 ng/mL (49 ng/mL, unbound) and AUC_{24} of 10,100 ng•h/mL (396 ng•h/mL, unbound) for males and females, respectively. The NOAEL in the 16-week study in monkeys was 30 mg/kg/day for both sexes with associated total C_{max} of 30,600 ng/mL (293 ng/mL, unbound) and total AUC_{24} of 218,000 ng•h/mL (2080 ng•h/mL, unbound).

In the rat CNS Safety Pharmacology study, higher numbers of vertical movements were noted in all dose groups (in a non-dose-dependent manner) compared with control animals. There were no other findings noted in that study on other measures of CNS activity (horizontal movements and functional observational battery), and there were no CNS-related findings in monkey or rat toxicology studies of up to 16 weeks in duration. From the above, it is suggested that these findings are not likely to lead to adverse events of concern in clinical trials.

Based on the nonclinical toxicity studies conducted, the kidney is considered a potential target based on moderate degeneration/regeneration of renal tubules in a single female monkey at 90 mg/kg/day in the 2 week toxicity study in monkeys with the finding associated with minimal increase in blood urea nitrogen (BUN); however, these findings were not seen in the 16 week toxicity study in monkeys at the same dose (90 mg/kg/day). Additionally, observed adverse microscopic findings in the lung, skin, nonglandular gastric mucosa (rats) and non-adverse findings in the Harderian (rats) and Meibomian glands (monkeys), and in platelet production (monkeys), were likely the result of exaggerated pharmacology and fatty acid deficiency.

In embryo-fetal development (EFD) studies, PF-05221304 resulted in fetal skeletal variations (rats and rabbits) plus fetal external and skeletal malformations (rabbits). In a fertility and early embryonic study in rats, all mating and fertility parameters were similar for dose groups up to the highest dose of 30 mg/kg/day, and there were no effects on estrous cycling or ovarian or uterine parameters in females, although female rats had lower weight gain before mating and during gestation, which was considered adverse. There were no effects on early embryonic survival, or reproductive organ weights or sperm parameters in the males.

In a phototoxicity study in pigmented rats, there were no clinical signs or skin reactions indicative of phototoxicity in the pigmented or non-pigmented skin sites; as well as no changes in ophthalmology parameters or light microscopic findings in the eye (cornea, lens, and retina), at all of the PF-05221304 doses tested.

1.3.2. Clinical Experience with PF-05221304

As of issuance of this protocol, a single clinical study (C1171001) has been completed with PF-05221304. Four additional studies are ongoing: a 16-week clinical study (C1171002) in subjects with NAFLD, a single dose study evaluating the effect of hepatic impairment on pharmacokinetics (PK) (C1171006), a single dose absorption, metabolism and excretion study (C1171010) and a fixed sequence combination study to evaluate pharmacokinetic drug-drug interaction between PF-05221304 and PF-06865571 in healthy subjects (C3711002; Section 1.5.2). In C1171001, a total of 96 (93 male and 3 female) healthy adult subjects were randomized. Overall, 82 subjects (85%) were exposed to at least a single oral dose of PF-05221304; with 56 of these subjects exposed to repeated doses of PF-05221304 for up to 14-days. Single oral doses (from 1 mg to 240 mg) and repeated total daily doses (from 2 mg/day to 200 mg/day administered once-daily or every 12 hours) were found to be well-tolerated with an acceptable safety profile. Over this dose range evaluated, while the maximum tolerated dose (MTD) was *not* identified, higher doses were not assessed either because the a priori identified pharmacokinetic (PK) stopping limit was achieved (single dose) *or* near complete inhibition of hepatic DNL was observed (with repeated dosing regimens evaluated).

In the clinical program to date, there have been no serious adverse events (SAEs), no treatment-emergent adverse events (TEAEs) of 'severe' intensity, and no apparent dose-related increase in frequency or severity of TEAEs across the 240-fold (single) and 100-fold (repeated) dose range studied. All of the TEAEs were 'mild' in intensity except 1 TEAE of 'platelet count decreased' deemed to be of 'moderate' intensity; this resulted in premature withdrawal of 1 subject following 13 (of 14) days of PF-05221304 dosing at 100 mg every 12 hours (Q12hr) (200 mg/day), the highest repeated dose evaluated. This subject was asymptomatic with no signs or symptoms of platelet dysfunction and the decrease in platelet count did not meet criteria for thrombocytopenia (defined as $<100{,}000/mm^3$). The platelet count increased towards baseline by 72 hours post last dose and was back to baseline by 10 days post last dose.

Upon single dose administration, the only TEAE reported by more than 1 subject was upper respiratory tract infection (1 subject while on placebo and 2 subjects while receiving 100 mg). Furthermore, with repeated dosing, the only TEAE reported by more than 2 subjects exposed to PF-05221304, across the entire dose range evaluated, was headache. All TEAEs were self-limiting requiring isolated use of concomitant medications and/or non-drug treatments to manage them.

Across the other safety-related data collected, drug-related, laboratory parameter changes were observed although none were remarkable following single dose administration of PF-05221304. Upon repeated dose administration of PF-05221304, identified adverse drug reactions (ADRs) included elevation in blood triglycerides and reduction of platelet count. This included a gradual increase in fasting and post-prandial serum triglycerides with repeated doses ≥40 mg/day with effect plateauing over the 14-day dosing period. At steady-state, the increase in mean fasting serum triglycerides (placebo-adjusted change from baseline) ranged from 35%-50% at doses ≥40 mg/day; while increases in weighted-mean ($AUC_{24}/24$) serum triglycerides (placebo-adjusted change from baseline) ranged from 20%-60%, at these same doses. At the doses ≥60 mg/day, a gradual decrease in platelet count was observed with repeated doses over the 14 day dosing period. This observation was not noted at PF-05221304 doses up to 40 mg/day and no signs or symptoms of platelet dysfunction were apparent based on the safety assessments performed. These ADRs have not been observed with administration of single oral doses as high as 240 mg. There were no apparent abnormalities noted in the other safety-related assessments such as blood pressure and cardiac conduction intervals [assessed on 12-lead electrocardiograms (ECGs)].

The plasma PK of PF-05221304 following oral administration suggests a moderate rate of absorption with a median time to maximum plasma concentration (T_{max}) ranging from 3 to 5 hours, following repeated dosing with the morning meal. Food (high-fat/high-caloric meal) had no clinically relevant effect on exposure which decreased slightly [area-under-the-curve to infinity (AUC_{inf}) by ~10% and C_{max} by ~25%], while rate of absorption was delayed with T_{max} of 2.5 hours (dosing in fasted state) moving out to 5 hours (when dosing occurred with food). After attainment of C_{max}, the disposition of PF-05221304 showed a decline with the half-life of PF-05221304 being independent of dose, and ranging from approximately 13 to 18 hours. Following single oral doses, the plasma PK parameters showed low-to-moderate variability with % Coefficient of Variation (CV) for AUC_{inf} ranged from 16% to 36% and from 17 to 25% for C_{max}. Following single and multiple oral doses, mean apparent clearance (CL/F) ranged from 15 to 26 mL/min and mean volume of distribution (Vz/F) ranged from 20 to 31 L. PF-05221304 has been determined to be highly bound to plasma protein in humans. Less than 1% of the oral dose of PF-05221304 was excreted unchanged in the urine, indicating that renal clearance is not a major clearance mechanism for PF-05221304.

Preliminary assessment of circulating metabolites suggests no concern of metabolites reaching exposures where Metabolites in Safety Testing (MIST) criteria need to be considered.

1.4. Background Information for PF-06865571

1.4.1. Nonclinical Experience with PF-06865571

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 neuro-pulmonary 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 twice daily [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 mouse fibroblasts. At this time, it is not known whether PF-06865571 can cause fetal harm when administered to pregnant women. Animal reproductive studies have not been conducted with PF-06865571. It is also not known whether PF-06865571 can affect male or female fertility, or whether PF-06865571 is secreted in human milk.

The NOAELs in the 6-week studies were the highest dose levels tested, 1000 (500 BID) mg/kg/day with associated unbound C_{max} and area under the curve over 24 hours (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•h/mL (ie, NOAEL exposures observed in rats).

1.4.2. Clinical Experience with PF-06865571

As of issuance of this protocol, three clinical studies have completed dosing with PF-06865571: C2541001, C2541002, and C2541003. C2541001 was the first study in which PF-06865571 was administered to human subjects and was an investigator- and subject-blind, sponsor-open, randomized, placebo-controlled, single ascending, oral dose, 2-cohort, interleaving design with placebo substitution, 4-period crossover study in which 17 healthy adult subjects were exposed to at least one dose of PF-06865571 ranging from 5 mg to 1500 mg. C2541002 was the first clinical trial designed to administer repeated (up to 14 days) oral doses of PF-06865571 in the fed state to human subjects. In C2541003, PF-06865571 pharmacokinetics (PK) of immediate release (IR) and modified release (MR) tablets of PF-06865571 was being compared to IR oral suspension under fed conditions. C2541005 is ongoing and is a Phase 1b, randomized double-blind (sponsor-open), placebo-controlled parallel group study designed to assess the safety, tolerability pharmacodynamics and pharmacokinetics of multiple oral doses of PF-06865571 for 2 weeks in adults with NAFLD.

In C2541001, PF-06865571 was administered as an immediate release suspension. PK data for 7 dose levels ranging from 5 mg to 1500 mg are presented below in Table 2. PF-06865571 was well tolerated with an acceptable safety profile, and there were no serious adverse events (SAEs) reported. A total of 16 adverse events (AEs) which were deemed

mild, were reported in C2541001, for subjects receiving active drug or placebo. No clinically significant trends in safety laboratory parameters, creatinine levels, ECGs, and vital signs were observed over the range of doses administered in C2541001. The maximum tolerated dose was not identified.

Following administration of single oral doses of PF-06865571 under fed conditions, median time for C_{max} (T_{max}) ranged from 1.5 to 4 hours across the dose groups. Approximate dose-proportional increases in C_{max} and AUC_{24} were observed between the 5 mg and 1500 mg doses. Under fed conditions, the mean terminal $t_{½}$ ranged from 1.5 to 5.2 hours. At the 1000 mg dose level, exposures under fasted condition were approximately 2-fold lower than those in the fed state. Median PF-06865571 T_{max} occurred earlier in the fasted state, compared to dosing under fed conditions (1 hour versus 4 hours). In addition, the terminal elimination half-life ($t_{½}$) under fasted conditions was more variable than under fed conditions.

Table 2. Summary of Plasma PF-06865571 PK Parameters Following Single Oral Doses in C2541001

	Parameter Summary Statistics[a] for PF-06865571 by Treatment							
Parameter (units)	**5 mg Fed**	**15 mg Fed**	**50 mg Fed**	**150 mg Fed**	**500 mg Fed**	**1000 mg Fed**	**1500 mg Fed**	**1000 mg Fasted**
N	6	6	6	5	6	6	5	6
AUC_{inf} (ng•hr/mL)	64.69 (20)	281.7 (31)	742.3 (21)	3354 (29)	9738 (21)	33160 (25)	39040 (17)	20120 (13)
AUC_{last} (ng•hr/mL)	63.92 (21)	279.3 (30)	738.3 (21)	3354 (29)	9736 (21)	33120 (25)	38970 (17)	19470 (11)
C_{max} (ng/mL)	17.87 (25)	73.01 (27)	193.2 (29)	785.7 (30)	1820 (26)	5257 (24)	5356 (19)	3470 (20)
T_{max} (hr)	2.00 (0.500-4.00)	1.50 (0.500-3.00)	2.00 (1.00-4.00)	3.00 (2.00-4.00)	3.00 (2.00-4.00)	4.00 (3.00-6.00)	4.00 (3.00-6.00)	1.00 (1.00-2.02)
$t_{½}$ (hr)	1.450 ± 0.222	1.638 ± 0.129	1.630 ± 0.552	2.552 ± 0.401	3.365 ± 1.126	4.693 ± 1.681	5.220 ± 3.137	10.32 ± 6.95

Abbreviations: %CV = percent coefficient of variation; hr = hour; N = number of subjects in the treatment group and contributing to summary statistics; PK = pharmacokinetic(s); SD = standard deviation.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.

Clinical data from the C2541002 study are available. Following 14 days of dosing of PF-06865571 up to 600 mg every 8 hours (Q8hr) or placebo to healthy subjects (n=60), there were a total of 112 AEs, a majority (103/112) of which were mild in intensity. Of the AEs of moderate intensity, 2 AEs were due to venipuncture, and other moderate AEs were isolated occurrences and included nausea, vomiting, headache, penile discharge, generalized pruritus without visible skin changes and presence of white blood cells in the urine. There was no evidence of increasing incidence or severity of AE with increasing dose.

There was one serious adverse event (SAE) in C2541002. One subject who was assigned to receive 600 mg PF-06865571 Q8hr in Cohort 4 was noted to have atrial fibrillation detected by ECG on Day 7. This episode of atrial fibrillation was not associated with any symptoms or adverse changes in blood pressure and resolved spontaneously within 24 hours. This episode prompted a brief hospitalization for less than 24 hours and was determined to be a SAE, and the subject discontinued dosing on Day 7. The investigator considered the event to be possibly related to study treatment, and the subject was withdrawn from the study. Dosing for the remainder of subjects in this cohort was halted on Day 8, per protocol. After investigator and Sponsor's review of clinical data, dosing was resumed in a subsequent cohort (Cohort 5) at 400 mg Q8hr for 14 days. After review of the clinical data of Cohort 5, Cohort 6 was administered 600 mg Q8hr for 14 days. This cohort completed dosing for the planned period of 14 days.

No clinically-significant trends in safety laboratory parameters, ECGs, or vital signs have been observed in clinical studies to date. However, preliminary data indicate that creatinine levels increased slightly with dose. At doses of 100 mg Q8hr and above, median creatinine levels increased by approximately 0.15 to 0.2 mg/dL compared to baseline, but returned to baseline levels at follow-up. The organic cation transporter 2 (OCT2) and/or multi-drug and toxin extrusion protein (MATE) inhibition by DGAT2 has been shown to affect creatinine levels.[16] Therefore, these changes are not necessarily reflective of changes in glomerular filtration rate (GFR) and instead may be due to OCT2 and/or MATE inhibition. Cystatin C levels, a marker of kidney function whose levels are not affected by OCT2/MATE inhibition, were measured in C2541002 and review of these data demonstrated no clear changes.

Based on overall AE and safety laboratory assessment, PF-06865571 was generally safe and well tolerated at the doses tested in study C2541002.

Steady state (Day 14) PK revealed an approximately dose proportional increase in PF-06865571 exposure. Steady state appeared to be attained by Day 1 due to the short elimination half-life. The median peak to trough ratio (PTR) was approximately 10-fold across the cohorts. A summary of multiple-dose PK data in C2541002 is presented in Table 3. Less than 2% of the total dose was eliminated renally across the dose range evaluated.

Table 3. Summary of Preliminary Steady State (Day 14) Plasma PF-06865571 PK Parameters Following Multiple Oral Doses in C2541002

Parameter (units)	30 mg Q8hr	100 mg Q8hr	240 mg Q8hr	400 mg Q8hr	600 mg Q8hr
C_{max} (ng/mL)	171.5 (38)	665.6 (43)	1520 (29)	2598 (22)	3527 (36)
T_{max} (hr)	2.03 (1-3.02)	2.01 (1-3)	2.5 (1-3)	2 (2-3)	3.0 (1.05-4)
AUC_{tau} (ng•hr/mL)	652.5 (36)	2619 (47)	5717 (32)	10,830 (15)	17010 (38)
$t_{1/2}$ (hr)	3.294 (46)	4.365 (48)	4.096 (13)	3.840 (27)	6.916 (33)
PTR	10.85 (58)	10.15 (62)	9.693 (65)	8.988 (53)	5.178 (49)

Geometric mean (%CV) for C_{max} and AUC. Median (range) for T_{max} and arithmetic mean (%CV) for $t_{1/2}$; NA- not available; All values reported as below limit of detection (BLQ) have been replaced with zero for all calculations.

Biomarker data used to assess potential for cytochrome P450 (CYP)3A induction (plasma 4β-hydroxycholesterol/cholesterol and urinary 6β-hydroxycortisol/cortisol ratios) indicate no clinically meaningful changes from baseline relative to placebo. Additionally, PF-06865571 Day 14 exposure was approximately dose proportional in C2541002, indicating no auto-induction of metabolism of PF-06865571 with multiple oral doses. Together, these data suggest that PF-06865571 is not a clinically meaningful inducer of CYP3A.

In addition, the potential of PF-06865571 to inhibit OCT2/MATE was assessed in C2541002 by evaluation of renal clearance of N-methylnicotinamide (NMN), an endogenous substrate for OCT2 and MATE transporters. PF-06865571 doses of 400 mg and 600 mg Q8hr, but not lower doses, appeared to have numerically greater reductions from baseline in renal clearance of NMN compared with placebo suggesting potential inhibition of OCT2/MATE transporters. These changes are consistent with the *in vitro* data indicating that PF-06865571 may be an OCT2/MATE1 inhibitor.

Study C2541003 was a Phase 1, open-label study in healthy subjects to investigate the PK of PF-06865571 following single oral administration of IR and MR tablets compared to oral suspension under fed conditions. A single oral dose of 150 mg PF-06865571 was administered as IR suspension, IR tablets, and slow and fast release MR tablets under fed conditions in order to mimic the anticipated conditions of actual clinical use. In this study, PF-06865571 demonstrated an acceptable safety and tolerability profile. PF-06865571 C_{max} and AUC values from IR suspension and tablets were similar to each other and met the bioequivalence (BE) criteria.

1.5. Background Information on PF-05221304 and PF-06865571 Combination

1.5.1. Non-Clinical Experience with Combination of PF-05221304 and PF-06865571

Platelet lowering is thought to be a class effect of ACC inhibition resulting from significant inhibition of DNL in the bone marrow leading to impaired megakaryocyte (MK) maturation.

Consistent with this information, reductions in platelets have been observed as a non-adverse event in monkeys with PF-05221304. However, reductions in platelet counts were not observed in cynomolgus monkey toxicology studies with the DGAT2 inhibitor PF-06865571, or in clinical studies with that compound. Monkeys were selected for combination toxicity testing because monkeys are sensitive to the effects of PF-05221304 on platelets, whereas, rats are not. In addition, monkeys are also a relevant species to test any impact of DGAT2 inhibition on PF-05221304 platelet lowering.

A pivotal 6-week repeat-dose toxicity study was conducted in cynomolgus monkeys with PF-05221304 and PF-06865571, alone and in combination. In this study, monkeys were administered 30 or 60 QD (quodque die, (once daily)) mg/kg/day PF-05221304 alone, 30 or 60 (QD) mg/kg/day PF-05221304 in combination with 300 (150 BID) mg/kg/day PF-06865571, or 300 (150 BID) mg/kg/day PF-06865571 alone. Test-article-related findings in the 60 (QD) mg/kg/day PF-05221304 alone and 60 (QD) mg/kg/day PF-05221304 in combination with 300 (150 BID) mg/kg/day PF-06865571 consisted of adverse body weight

loss and dehydration, and non-adverse changes in hematology and clinical chemistry parameters.

Co-administration of 300 (150 BID) mg/kg/day PF-06865571 did not alter the toxicity associated with 60 (QD) mg/kg/day PF-05221304. The toxicokinetics of PF-06865571 and PF-05221304 were not affected by co-administration. The oral administration of up to 60 (QD) mg/kg/day PF-05221304 and/or 300 (150 BID) mg/kg/day PF-06865571 alone or in combination to cynomolgus monkeys for 6 weeks did not result in mortality or any test article-related changes in mean body weights or mean body weight changes, ECG parameters, mean organ weight ratios, coagulation or urinalysis test results, and no test article-related macroscopic or microscopic observations were noted. The few test article-related clinical pathology findings noted on Day 43 were all considered non-adverse due to their small magnitude and lack of correlative clinical or microscopic findings. The non-adverse test article-related hematology finding was mildly to moderately decreased platelet count (0.37x-0.55x baseline) in 1 male and 1 female administered 60 (QD) mg/kg/day PF-05221304 alone and 1 male (Animal P0503) administered 60 (QD) mg/kg/day PF-05221304 with 300 (150 BID) mg/kg/day PF-06865571. The non-adverse, test article-related clinical chemistry findings were minimally decreased albumin (0.81x-0.85x baseline) in animals administered 60 (QD) mg/kg/day PF-05221304 alone or with 300 (150 BID) mg/kg/day PF-06865571 and mildly decreased cholesterol (0.55x-0.61x baseline) in animals administered 30 (QD) or 60 (QD) mg/kg/day PF-05221304 with 300 (150 BID) mg/kg/day PF-06865571.

In monkeys, doses of 30 (QD) mg/kg/day PF-05221304 and 300 (150 BID) mg/kg/day PF-06885571, alone or in combination, were considered the no observed adverse effect levels (NOAEL) for each respective and combined test articles based on a lack of adverse findings. The anticipated exposures of PF-05221304 at 15 mg BID in this study are 122-fold and 29-fold lower (C_{max} and AUC_{24}, respectively) than the NOAEL (30 mg/kg (QD) PF-05221304 + 300 mg/kg (BID) PF-06865571) in the 6-week combination toxicology study in monkeys. Similarly, the anticipated exposures of PF-06865571 at 300 mg BID in this study are 3.7 and 6.2-fold lower than the 6-week monkey NOAEL. The dose of 60 (QD) mg/kg/day PF-05221304, alone or with 300 (150 BID) mg/kg/day PF-06865571, was adverse due to the severity of body weight loss and/or dehydration with concomitant fecal abnormalities for 1 male in each group that required supportive fluid therapy and dose suspension for 1 male.

1.5.2. Clinical Experience with Combination of PF-05221304 and PF-06865571

At the issuance of this protocol, C3711002, the first clinical study testing co-administration of PF-05221304 and PF-06865571, is underway. C3711002 is designed as a Phase 1, open label, multiple dose, 2-cohort, non-randomized, fixed-sequence study to evaluate the pharmacokinetic drug-drug interaction (DDI) between PF-05221304 and PF-06865571, and safety and tolerability of in healthy adult subjects. Each of the Investigational Products (IPs) is being administered orally twice daily.

A total of 16 subjects were enrolled in this study (N=7 in Cohort 1, N=9 in Cohort 2). In Cohort 1, subjects received PF-05221304 15 mg Q12hr (every 12 hours) on Days 1-7 and PF-05221304 15 mg Q12hr plus PF-06865571 300 mg Q12hr on Days 8-13. On Day 14, subjects received PF-05221304 15 mg plus PF-06865571 300 mg once (AM only). In Cohort 2, subjects received PF-06865571 300 mg Q12hr on Days 1-7 and PF-05221304 15 mg Q12hr plus PF-06865571 300 mg Q12hr on Days 8-13. On Day 14, subjects received PF-05221304 15 mg plus PF-06865571 300 mg once (AM only). All doses in this study were administered with food. Pharmacokinetic parameters were compared on Day 14 (combination) versus Day 7 (each agent administered alone). Additionally, safety and tolerability were assessed for each subject. C3711002's dosing period is completed and a summary of the available preliminary data is provided below.

Safety Summary

In Cohort 1, after 7 days of dosing PF-05221304, followed by 7 days of combined dosing of PF-05221304 and PF-06865571, a total of 9 AEs were reported in 5 subjects, with 6 AEs categorized as mild and 3 as moderate in severity.

The 3 AEs of moderate severity were reported in one subject and corresponded to concurrent elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT). The subject started the study with a minor elevation in baseline ALT (59 Units/Liter (U/L)). Asymptomatic increases in ALT and AST were detected on scheduled safety labs on Day 7 while dosing PF-05221304 alone. ALT peaked at 187 U/L (3.8x upper limit of normal (ULN)) and AST peaked at 116 U/L (2.9x ULN) on Day 8, prompting precautionary discontinuation of the subject from the study on Day 9, after completing one full day of dosing of the PF-05221304 and PF-06865571 combination. Total bilirubin and alkaline phosphatase remained normal. Upon further review of the pre-randomization labs, it was found that the subject had high GGT at baseline (123 U/L; Normal Limit Range=0-73 U/L). The subject's liver function tests returned to baseline values on Day 22 of the study. The subject remained asymptomatic throughout the entire period.

Preliminary analysis of safety laboratory data from Cohort 1 was notable for the following observations. A mild elevation in ALT (~1.4x ULN) was observed in 2 other subjects on Day 7 of the monotherapy dosing period with PF-05221304. In both cases ALT returned within normal range with continued dosing, which included completion of the 7-day period of combined dosing with PF-05221304 and PF-06865571. These elevations were not considered as AEs.

Two subjects had increases in triglycerides exceeding ULN with peak values at Day 10 of 212 mg/dL and 255 mg/dL respectively. Both subjects trended down on Day 14, one subject with continued dosing. The second subject is the same one that was discontinued as a precautionary measure due to ALT elevation >3 x ULN (see above).

One subject with a baseline platelet count of 156,000/mm^3 (lower limit of normal (LLN)=150,000/mm^3) had platelet count dip slightly below normal with a nadir of 138,000/mm^3 and remained stable at approximately that level throughout the study. Platelet values for all other subjects remained within normal limits.

A slight trend for increase in serum creatinine was observed after Day 7, which remained stable at Day 14, returning towards baseline at follow-up. All values remained within the normal range for the whole period of observation. Cystatin C remained within the normal range with minor fluctuations during this period. Thus, these observations are interpreted as consistent with an effect of PF-06865571 to inhibit OCT2/MATE and not necessarily reflective of changes in glomerular filtration rate or renal function. No clinically significant trends in other safety laboratory parameters, ECGs or vital signs were observed in Cohort 1.

In Cohort 2, after 7 days of dosing PF-06865571, followed by 7 days of combined dosing of PF-06865571 and PF-05221304, a total of 17 AEs were reported in 7 subjects, with 13 AEs categorized as mild and 4 as moderate in severity. Two of the 4 moderate severity AEs corresponded to a concurrent episode of, respectively, nausea and vomiting in one subject. The other 2 moderate severity AEs corresponded to left back pain and headache in another subject. All AEs resolved without sequelae.

Preliminary analysis of safety laboratory data from Cohort 2 was notable for the following observations. One subject had a mild elevation in ALT to 58 U/L (ULN<49 U/L), detected on scheduled safety laboratories in Day 7 while receiving PF-06865571. ALT increased slowly with peak value of 99 U/L on Day 10, then decreasing towards baseline with continued dosing, which included completion of the 7-day period of combined dosing with PF-06865571 and PF-05221304. ALT values reached baseline by Day 21.

A slight trend for increase in creatinine was observed from baseline to Day 7 with dosing of PF-06865571 alone, with average increase in creatinine of approximately 0.05 mg/dL and remaining stable through the rest of the dosing period. All creatinine values remained within normal limits and values were trending back to baseline by Day 22 (follow up visit). Cystatin C trended slightly up with all values remaining well within normal limits. These observations are again interpreted as consistent with an effect of PF-06865571 to inhibit OCT2/MATE and not necessarily reflective of changes in glomerular filtration rate. Three subjects in this cohort had increases in fasting triglycerides exceeding ULN with peak values at Day 14 of 166 mg/dL, 196 mg/dL and 223 mg/dL respectively. All subjects trended down on Day 22 with continued dosing.

No clinically significant trends in other safety laboratory parameters, ECGs or vital signs were observed in Cohort 2.

No SAEs have been reported in the study, to date.

PK Summary

Preliminary PF-05221304 plasma PK parameters when administered alone (Day 7) or with PF-06865571 (Day 14) have been summarized below in Table 4. PF-05221304 AUC_{12} was modestly lower (~19%) when administered with PF-06865571 versus alone.

Table 4. PF-05221304 PK Parameters following Administration of PF-05221304 Alone (15 mg BID) or with PF-06865571 (300 mg BID) in C3711002

Parameter (units)	PF-05221304 Alone (Day 7)	PF-05221304 + PF-06865571 (Day 14)	GMR (90%CI)
AUC_{tau} (ng•hr/mL)	12130.35 (25.80%)	9482.76 (23.03%)	0.81(0.74,0.88)
C_{max} (ng/mL)	1337.03 (25.08%)	1128.14 (19.94%)	0.88(0.80,0.98)
T_{max} (hr)	4.00 (2.00-6.00)	2.00 (1.50-4.00)	NA

Geometric mean (%CV) for C_{max} and AUC. Median (range) for T_{max}; NA = not applicable;
GMR=Geometric Mean Ratio (Day 14/Day 7); CI= confidence interval.

Preliminary PF-06865571 plasma PK parameters of administered alone (Day 7) or with PF-05221304 (Day 14) have been summarized in Table 5. PF-06865571 pharmacokinetics are essentially unchanged when administered with PF-05221304 versus alone.

Table 5. PF-06865571 PK Parameters following Administration of PF-06865571 Alone (300 mg BID) or with PF 05221304 (15 mg BID) in C3711002

Parameter (units)	PF-06865571 Alone (Day 7)	PF-06865571 + PF-05221304 (Day 14)	GMR (90%CI)
AUC_{tau} (ng•hr/mL)	8716.33 (18.73%)	9436.24 (33.88%)	1.08(0.97,1.21)
C_{max} (ng/mL)	2385.54 (9.56%)	2579.70 (20.71%)	1.08(0.98,1.19)
T_{max} (hr)	2.00 (1.00-4.00)	2.00 (1.00-2.00)	NA

Geometric mean (%CV) for C_{max} and AUC. Median (range) for T_{max}; NA = not applicable;
GMR=Geometric Mean Ratio (Day 14/Day 7); CI= confidence interval;

Additional information for PF-05221304 and PF-06865571 may be found in the single reference safety document (SRSD) for each compound, which are the Investigators' Brochures (IBs) for PF-05221304 and PF-06865571, respectively.

1.6. Study Rationale

The objective of this study is to assess the effect of PF-05221304 alone, PF-06865571 alone, the co-administration of PF-05221304 and PF-06865571, or placebo on whole liver fat in subjects with NAFLD. In addition, this study will evaluate the safety and tolerability of co-administration of PF-05221304 and PF-06865571 along with the effects on selected pharmacodynamics (PD)/exploratory parameters, compared to administration of PF-05221304 alone, PF-06865571 alone, and placebo in adults with NAFLD.

1.6.1. Design Rationale

To address the potential effect of PF-05221304 and PF-06865571 co-administration on liver fat, the eligible population for study enrollment is subjects with NAFLD, defined as having liver fat ≥8%, as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) at Screening Visit 3. In an effort to help identify these subjects, evidence of concomitant medical conditions known to predispose subjects to NAFLD, including features of metabolic syndrome or T2DM will be utilized. FibroScan® assessments will be done at Visit 1 (Screen 1) and Visit 2 (Screen 2) to help initially estimate liver fat using a more scalable and cost-efficient approach than MRI-PDFF. Subjects who meet all eligibility criteria for the study during Screen 1 will proceed to Screen 2 for an additional liver fat approximation by FibroScan®. Two assessments using FibroScan will be used because of the variability in fat determination with Controlled Attenuation Parameter (CAP™), measure of liver fat content. These assessments will provide a more accurate initial estimate of liver fat prior to MRI-PDFF. Subjects will then undergo liver fat assessment by MRI-PDFF (Screen 3) for confirmatory purposes.

For the assessment of liver fat (either via FibroScan® or MRI-PDFF), subjects will be required to fast (water permitted) for ≥4 hours given the ability of food to impact the results. In order to limit measurement variability, the nominal time for FibroScan® and MRI-PDFF assessments will be standardized. Baseline assessments for MRI-PDFF and FibroScan® (Visits 5 and 6, respectively) should fall within a practical window (±2 hours) relative to clock time of the initial screening visit for each assessment. All post-randomization assessments for both MRI-PDFF and FibroScan® should occur within a practical window (±2 hours) relative to clock time of the baseline visit for each assessment (ie, Visit 5 and 6, respectively).

A fixed, single-blind placebo run-in period of approximately 14 days (from Visit 4 to Visit 6) following confirmation of eligibility and prior to randomization is included to familiarize subjects with the study treatment regimen and to exclude subjects who are not compliant with single-blinded placebo administration prior to randomization at Visit 6. To date, clinical experience with PF-05221304 and PF-06865571 co-administration is limited to a PK drug-drug interaction (DDI) study (C3711002) with a total of 1 week duration of combined drug exposure in an inpatient setting. In this study, with longer and predominantly outpatient dosing in a patient population, close safety monitoring will be implemented with frequent (every 2 weeks) outpatient visits post randomization, including an additional, early visit at Day 5 (Visit 7).

Total duration of PF-05221304 and PF-06865571 co-administration in this study will be approximately 6 weeks, supported by a completed 6-week non-clinical combination toxicity study in monkeys. This duration is expected to allow assessment of effects of co-administration of PF-05221304 and PF-06865571 on liver fat content, as well as on safety and tolerability of these agents.

In this study PF-05221304 and PF-06865571 co-administration will be required to occur twice daily with food (breakfast and dinner).

This study is designed to assess the effect of PF-05221304 and PF-06865571 on liver fat and other PD biomarkers that are intended to provide insight into metabolic pathways related to ACC and DGAT2 inhibition. Specifically, the study will evaluate the effect of PF-05221304 and PF-06865571 combination on liver fat and liver function [ie, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and gamma-glutamyl transferase (GGT)], glycemic parameters, and fasting lipids including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs). In addition, effect on other PD parameters [ie apolipoproteins A1, B (total), C3, CCI , proprotein convertase subtilisin/kexin type 9 (PCSK9) CCI and certain NASH-related biomarkers] will be assessed. CCI

CCI

CCI

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. In accordance with reported literature on OCT2/MATE inhibition, minor increases in serum creatinine have been observed in C2541002, a 2-week multiple dose ascending study for PF-06865571, with very limited 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).

Interim analysis (IA) may be performed [refer to Section 9.8] to permit a review of safety and pharmacodynamics of the population enrolled, amongst the planned activities.

1.6.2. Rationale for Population Enrolled

The study population included in this study will be overweight or obese subjects (body mass index [BMI] ≥25 kg/m^2) with clinical indicators of metabolic syndrome and/or T2DM.

Although NAFLD is a condition with excessive fat accumulation in the liver defined as ≥5%, this study will enroll subjects with liver fat values ≥8% at screening to allow for potential measurement variability and help ensure baseline liver fat values are likely to be ≥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 (Visit 6) based on

MRI-PDFF (Screen 3) liver fat ranges of ≥8% to <15%; and ≥15% as a means of balancing liver fat content between dosing cohorts. A second-tier stratification will also be applied at randomization based on the presence or absence of T2DM (refer to Section 4.3 for additional details regarding stratification).

T2DM subjects will be permitted to be on a stable dose of up to 1 acceptable oral drug for glycemic control. These may include sulphonylureas, dipeptidyl peptidase-IV inhibitors (DPP-IVi) and meglitinides. However, thiazolidinediones (TZDs), glucagon-like peptide-1 receptor (GLP-1r) agonists and sodium-glucose co-transporter 2 (SGLT2) antagonists are not permitted given their reported anti-steatotic effect that may potentially confound the effect of study drugs on primary endpoint of this study. Metformin is not permitted due to the potential risk for OCT2/MATE inhibition by PF-06865571 resulting in a drug-drug interaction (DDI) potentially increasing metformin exposure. Refer to Section 5.8 for complete details regarding permitted and excluded concomitant medications.

Eligible women will be confirmed to be of non-childbearing potential since at the present time embryo-fetal developmental toxicology studies with PF-06865571 have not yet been conducted and exposure to PF-05221304 in embryo-fetal developmental toxicology studies has been shown to result in fetal skeletal variations (rats and rabbits) plus fetal external and skeletal malformations (rabbits). In eligible men, appropriate measures to minimize potential transfer of PF-05221304 or PF-06865571 via semen to a woman of childbearing potential are expected to be followed [refer to Section 4.4.4].

1.6.3. Dose Rationale

This study is planned as a 2x2 factorial, 4-arm, parallel group study with 1 placebo arm, 1 active dose arm of PF-05221304 (15 mg, Q12hr), 1 active dose arm of PF-06865571 (300 mg, Q12hr) and 1 active dose arm for co-administration of PF-05221304 (15 mg, Q12hr) and PF-06865571 (300 mg, Q12hr).

The objective of this study is to assess the effect of PF-05221304 alone, PF-06865571 alone, the co-administration of PF-05221304 and PF-06865571, or placebo on whole liver fat in subjects with NAFLD. Additionally, the study is designed to further characterize the safety and tolerability of PF-05221304 and PF-06865571 when co-administered versus each agent given alone. Lastly, the ability of PF-06865571 to mitigate possible increases in plasma triglycerides that are associated with PF-05221304 dosing when high levels of hepatic DNL inhibition are achieved will be explored.

As data are not available at this time regarding the effect of PF-06865571 on liver fat in patients with NAFLD, a dose was selected (300 mg BID) that is projected to achieve average daily concentration 4-fold higher than the projected unbound human efficacious concentration (C_{eff}) [120 nM (48.9 ng/mL)]. This dose is also the highest dose being examined in an ongoing 2-week study assessing the effect of PF-06865571 on liver TG in subjects with elevations in liver fat. A total daily dose 2 fold higher than the PF-06865571 dose proposed for this study has been well tolerated with an acceptable safety profile in the multiple ascending dose study (C2541002).

A dose of 15 mg BID was selected for PF-05221304 in this study. Although PF-05221304 has a pharmacokinetic half-life conducive to once daily dosing, a Q12hr dosing regimen was selected to match the profile of a combination product (Q12hr dosing likely needed due to short half-life of PF-06865571). The 15 mg Q12hr dose is expected to yield similar average daily hepatic *de novo* lipogenesis inhibition (88%) as the top dose of 50 mg QD in the ongoing 16 week Phase 2a study (C1171002) in subjects with elevated liver fat (90%). The dose of 15 mg Q12hr is approximately 6 fold less than the highest dose tested in C1171001 (100 mg Q12hr).

1.6.4. Rationale for Banked Biospecimen Collection

In this study, subject to regulatory and ethics approval/favorable opinion, an additional research component includes collection of blood for Prep D1.5, Prep B1.5, and Prep B2.5 (see Section 7.7) for possible exploratory analyses. These retained pharmacogenomic and biomarker collections will be undertaken as a means to enable the exploration of the contribution of genomic and other biomarker variations to the observed variability in PK of, and for response to, PF-05221304 and PF-06865571 and wider research investigation, as permitted by subject consent.

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) makes it possible to better understand the investigational product's (IP) mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS can also be used in research on non-alcoholic fatty liver disease or related metabolic disorders.

Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited by local regulations or ethics committee (EC) decision.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
To determine the effect of co-administration of PF-05221304 and PF-06865571 on whole liver fat compared to placebo, PF-05221304 administered alone, and PF-06865571 administered alone in subjects with NAFLD.	Relative change from baseline in whole liver fat at Day 42, as assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF).
Secondary Objective(s):	**Secondary Endpoint(s):**
To evaluate safety and tolerability of PF-05221304 and PF-06865571 co-administration compared to	Assessment of treatment-emergent adverse events (and serious adverse events), clinical laboratory tests

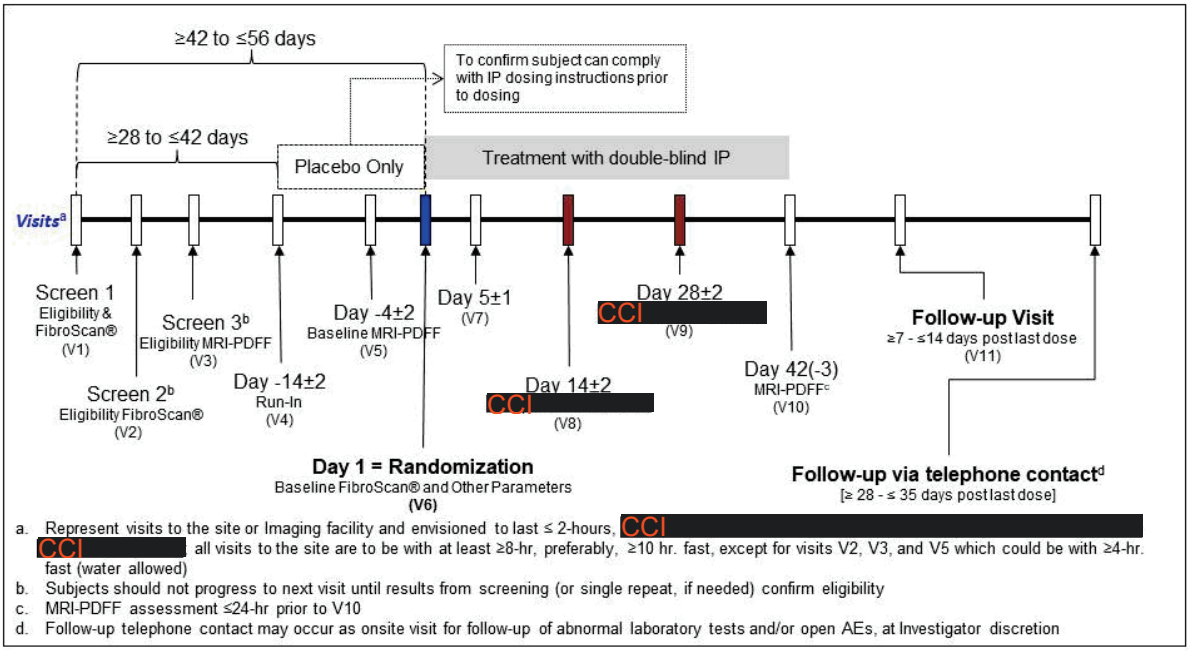
placebo, PF-05221304 administered alone, and PF-06865571 administered alone in subjects with NAFLD.	including lipids, vital signs, and 12-lead electrocardiograms.
Tertiary/Exploratory Objective(s):	**Tertiary/Exploratory Endpoint(s):**
To evaluate the effect of co-administration of PF-05221304 and PF-06865571, on liver function tests (LFTs) compared to placebo, PF-05221304 administered alone, and PF-06865571 administered alone in subjects with NAFLD.	Percent change from baseline at all time points for: • ALT, AST. • Alkaline Phosphatase. • Gamma-glutamyl transferase (GGT).
To evaluate effects of co-administration of PF-05221304 and PF-06865571 on lipids compared to placebo, PF-05221304 administered alone, and PF-06865571 administered alone in subjects with NAFLD.	Percent change from baseline at all time points for: • Triglycerides. • Total cholesterol, HDL-C, direct LDL-C, Total cholesterol/HDL-C ratio, and non-HDL-C.
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
[redacted]	[redacted]
To evaluate the PD effects of co-administration of PF-05221304 and PF-06865571 compared to placebo, PF-05221304 administered alone, and PF-06865571 administered alone, in adults with NAFLD.	Analyses for PD parameters: • % Change from baseline to Day 42 in Apolipoproteins (A1, B100 and C3). CCI [redacted] • % Change from baseline to Day 42 in plasma PCSK9. CCI [redacted]
CCI [redacted]	[redacted]
To collect banked biospecimen for exploratory research, unless prohibited by local regulation or ethics committee decision.	Collection of banked bio-specimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in Section 7.7

3. STUDY DESIGN

3.1. Study Overview

This is a randomized, double-blind (sponsor-open), placebo-controlled, 2x2 factorial, 4-arm (placebo, monotherapy of PF-05221304, monotherapy of PF-06865571 and combination of PF-05221304 and PF-06865571), parallel group study (Figure 1).

Figure 1. C3711001 Study Design



Determination of eligibility for this study will occur via a sequential, 3-step process, starting at the first screening visit (Screen 1). Subjects identified to be eligible based on Screen 1 AND Screen 2 procedures will proceed to Screen 3 to measure liver fat by MRI-PDFF. For a given subject, this 3-step eligibility assessment may take up to 6 weeks.

Once confirmed to be eligible based on results of Screen 3, subjects will progress to a Run-in period (Visit 4), at which time subjects will receive single-blind placebo for approximately 14 days to ensure compliance with the administration of IP. Approximately 4 days prior to randomization, subjects will report to the imaging center (Visit 5) to have a baseline MRI-PDFF scan performed. At Visit 6 (Day 1), subjects will be randomized to receive 1 of 4 blinded IP regimens (placebo, PF-05221304 monotherapy, PF-06865571 monotherapy, or PF-05221304 plus PF-06865571 combination) for a duration of up to 6 weeks (ie, 42 days). This study includes a total of 11 scheduled outpatient visits to the study site, including 4 visits to the imaging center, and a safety Follow-up telephone contact. The total participation, from Visit 1 (Screen 1) to Follow-up telephone phone call will be up to approximately 19 weeks.

Approximately 98 subjects (14 for the placebo group, 28 for each of the monotherapy groups and 28 for the combination group) will be randomized at approximately 30 sites (refer to Section 9.1).

Subjects who are noted to have non-evaluable baseline MRI-PDFF, as determined by the sponsor-identified central imaging vendor, should have their MRI-PDFF repeated once; if the images are still non-evaluable on single-repeat, the subject will be considered as screen failed; otherwise, there are no plans to replace subjects who are prematurely withdrawn.

3.2. Stopping Rules in Individual Subjects

At investigator discretion, for subjects' safety, dosing with any of the double-blinded investigational product(s) (ie, post randomization), may be stopped in an individual subject-either temporarily or permanently. Any treatment-related SAE will result in permanent discontinuation of the subject. Any open TEAEs must be followed to resolution or until such time that the event is viewed to have stabilized–refer to Section 8 for details. Of note, subjects who meet threshold for withdrawal based on platelet count (see Appendix 3) or fasting serum triglycerides (see Appendix 4), should not be re-challenged with investigational product. Additionally, a subject may not cross-over to another group, once randomized to a particular group.

An example where temporary discontinuation of dosing with investigational product(s) may be considered includes hospitalization with subsequent discharge within ≤7-days in stable medical condition, as determined by medically-qualified investigator. Examples where permanent discontinuation of dosing and withdrawal of the subject from the study is deemed appropriate, as determined by investigators' medical judgment, include:

- Hospitalization due to serious adverse event (SAE) resulting in clinical decompensation of the subject and necessitating continued inpatient stay for more than 7-days.

- Subjects observed to have a decline over time ultimately reaching the threshold of <75,000/mm^3 in platelet count –refer to Appendix 3 for additional guidance.

- Individual subjects with consistently increasing fasting serum triglycerides over time ultimately reaching the threshold of ≥800 mg/dL (9 mmol/L) –refer to Appendix 4 for additional guidance.

    - **Note**: In both cases of pre-identified laboratory thresholds listed above, 1 additional unplanned assessment may be warranted before permanent withdrawal if the threshold is observed to be met as an isolated occurrence relative to all prior results and subject is asymptomatic.

3.3. Considerations for Pausing or Stopping Treatment Arm or Trial Based on Observed Safety

A monthly blinded safety review, including laboratory values, vital signs, adverse events and SAEs will be conducted throughout the study. When approximately 50% of the planned number of subjects are randomized, the subsequent monthly safety review will assess whether ***either*** of the below conditions are met.

- More than 25% of subjects, develop a moderate or severe AE in the same system organ class (SOC);
- More than 25% of subjects meet the individual permanent discontinuation of dosing rules (Section 3.2).

If neither of these criteria is met the study will continue as planned, while continuing monthly blinded safety monitoring. If either criterion is met, an unblinded review by a pre-specified Internal Review Committee (IRC), independent from the study team, will be triggered. Based on their unblinded safety review the IRC will make a recommendation to the team to either continue the trial as designed, discontinue one or more of the active arms of the study, or stop the trial altogether.

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 into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Male subjects or female subjects of non-childbearing potential between the ages of 18 and 70 years, inclusive, at Screen 1.

Female subjects of non-childbearing 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.

4. At Screen 1 (Visit 1), total body weight of >50 kg (110 lbs) and a BMI ≥25 kg/m^2.

5. Subjects at Screen 1 (Visit 1), with a medical diagnosis of Type 2 Diabetes Mellitus (T2DM) being treated with no more than 1 acceptable oral antidiabetic drug (see Section 5.8.1 for acceptable versus prohibited medications);

OR

Subjects without a diagnosis of T2DM that meet **≥2** of the following 5 criteria commonly associated with metabolic syndrome:

- Fasting Plasma Glucose (FPG) ≥100 mg/dL (5.6 mmol/L);
- Documentation of at least stage 1 hypertension as demonstrated by a seated blood pressure (BP) ≥130/80 mmHg or medical history of hypertension actively treated with pharmacological agents;
- Fasting serum HDL-C <40 mg/dL (1 mmol/L) for males and <50 mg/dL (1.3 mmol/L) for females, or on pharmacological agents *with explicit purpose* to increase HDL-C (refer to Section 5.8.3 for acceptable versus prohibited medications);
- Fasting serum triglyceride (TG) ≥150 mg/dL (1.7 mmol/L), or on pharmacological agents *with explicit purpose* to decrease TG (refer to Section 5.8.3 for acceptable versus prohibited medications);
- Waist circumference ≥40 inches (102 cm) for males and ≥35 inches (89 cm) for females.
    - **Note:** For laboratory parameters, results must be as assessed by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed, at each of these 2 visits.

6. At Screen 1 (Visit 1), a CAP™ ≥280 dB/m via FibroScan® assessment.

7. At Screen 2 (Visit 2), a CAP™ ≥280 dB/m via FibroScan® assessment:

   - **Note (for #6 and #7)**: if the CAP™ value is in the range of 260-279 dB/m during Screen 1 or Screen 2, 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.

8. At Screen 3 (Visit 3), liver fat ≥8% 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.

4.2. Exclusion Criteria

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

1. Subjects with 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 investigational product administration 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.

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

   - Fasting TG >400 mg/dL;

   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma glutamyl transferase (GGT) >2.0x upper limit of normal (ULN);

   - Hemoglobin A1c (HbA1c) >7.0%;

   - Fasting plasma glucose >270 mg/dL (15.0 mmol/L);

   - Total bilirubin >1.5x ULN with a direct bilirubin ≥ ULN;

     - **Note**: Subjects with a history of Gilbert syndrome will be eligible for this study provided direct bilirubin level is ≤ ULN plus ALT meets inclusion criteria and alkaline phosphatase, hemoglobin, and reticulocyte count are ≤ ULN.

   - Albumin < lower limit of normal (LLN);

- Platelet count <0.95 x LLN;
- International normalized ratio (INR) ≥1.3.
    - **Note**: For ALT, AST, total bilirubin and INR, laboratory values should not meet exclusion criteria at **both** Screen 1 and at Visit 4.

3. A positive urine test for illicit drugs at Screen 1 (Visit 1), start of Run-in (Visit 4), or baseline (Visit 6).
    - **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 (Visit 1).
5. At Screen 1 (Visit 1), seated 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 (Visit 1), supine 12-lead ECG demonstrating a corrected QT (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 (Visit 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 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 prior to Screen 3, permitted to assess eligibility, if needed.
    - Hepatitis B virus (HBV), defined by presence of hepatitis B surface antigen (HepBsAg) or hepatitis B core Antibody (HepBcAb);
    - Hepatitis C virus (HCV), defined by presence of hepatitis C antibody (HCVAb);

- *irrespective of* 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;

    - 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 as these could interfere with the use of FibroScan®.

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-PDFF obtained at Screen 3 (Visit 3), by the Sponsor-identified central imaging vendor or subjects meeting criteria for contraindication for MRI-PDFF, including the following:

    - History of severe claustrophobia impacting ability to perform MRI-PDFF 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, as measured by the Hula-hoop test.

11. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing and until the on-site Follow up visit.

12. Subjects taking prohibited concomitant medication(s) or those unwilling/unable to switch to permitted concomitant medication(s) (refer to Section 5.8.).

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

14. Unwilling or unable to comply with the criteria in the Lifestyle Requirements section of this protocol.

15. 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 investigational product.

16. 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.

17. 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).

18. Subjects with known prior participation in a clinical trial involving PF-05221304 and/or PF-06865571 (ie received at least 1 dose of IP).

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 1:2:2:2 ratio (placebo:PF-05221304:PF-06865571:PF-05221304 plus PF-06865571 combination) prior to the first dose of IP, provided subjects satisfy all of the eligibility criteria outlined in Section 4.1 and Section 4.2.

- An attempt will be made to equally balance the number of subjects assigned to each treatment arm within stratum by utilizing a stratification scheme as follows. Subjects will be stratified at randomization (Day 1) by the MRI-PDFF liver fat measurement determined by the Sponsor-identified central imaging vendor of images obtained during Screen 3:
  - Screening liver fat ≥8% and <15%;
  - Screening liver fat ≥15%;
  - Subjects will then be stratified by the presence or absence of T2DM.

4.4. Lifestyle Requirements

After confirmation of eligibility at Screen 3 (Visit 3) and starting at Run-in (Visit 4), subjects will be instructed to maintain the guidelines described below for the duration of participation in the study. These guidelines must be reiterated on Day 1 (Visit 6) and during site visits thereafter. The following guidelines are provided.

4.4.1. Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) for at least 8, but preferably 10 hours, prior to any blood sample collections for clinical laboratory tests.
  - **Note**: Subjects must abstain from all food and drink (except water) for ≥4 hours prior to **ALL** liver fat assessments, including Screen 1 and Screen 2.
- Blinded IPs should be administered twice daily with morning and evening meals and should be separated by at least 8 hours.
- Subjects will be instructed to maintain their normal diet throughout participation in the study (ie through Visit 11).

4.4.2. Alcohol, Caffeine, and Tobacco

- Intake of alcohol is permitted in moderation as defined in Section 4.2.

- Consumption of caffeinated drinks and nicotine-containing products is permitted during participation in the study; however, there may be a need for brief interruption while at the site and/or Imaging facility, depending on local policy.

4.4.3. Physical Activity

- Subjects will be asked to not engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) within 48 hours before blood sample collections for clinical laboratory tests.

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 investigational product. 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 the subject or 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 subject or 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 post vasectomy 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 female partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the dose of investigational product (Day 1) and continuing for at least 28 days after the dose of IP(s).

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 investigational product 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. 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, investigational product 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 investigational product(s) are PF-05221304 and PF-06865571 and their matching placebo. These will be administered as oral tablets.

5.1. Allocation to Treatment

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (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 and dispensable unit (DU) or container number. The IRT system will provide a confirmation report containing the subject number, randomization number, and DU or container number assigned. 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.

Table 6. Study Treatment Regimen and Dispensing Schedule

Treatment Group	Treatment Regimen	Dosage[a] AM and PM
A	Placebo (PF-05221304) BID Placebo (PF-06865571) BID	3 x Placebo (PF-05221304) tablets PLUS 3 x Placebo (PF-06865571) tablets
B	15 mg PF-05221304 BID Placebo (PF-06865571) BID	3 x 5 mg PF-05221304 tablets PLUS 3 x Placebo (PF-06865571) tablets
C	Placebo (PF-05221304) BID 300 mg PF-06865571 BID	3 x Placebo (PF-05221304) tablets PLUS 3 x 100 mg PF-06865571 tablets
D	15 mg PF-05221304 BID 300 mg PF-06865571 BID	3 x 5 mg PF-05221304 tablets PLUS 3 x 100 mg PF-06865571 tablets
a: Dosing in AM (with breakfast) and PM (with dinner) will be same		

A computer generated randomization schedule will be used to assign approximately 98 subjects to one of the 4 treatment groups described in Table 6 in a randomization ratio of 1:2:2:2 for treatment groups A, B, C, and D respectively. The randomization number will be recorded in the case report form (CRF). The subject will receive the appropriate IP assigned by the IRT system.

In order to maintain the double-blind design:

- 5 mg PF-05221304 and matching placebo tablets will be the same size and shape; similarly, 100 mg PF-06865571 and matching placebo tablets will be the same size and shape.
- Each dose will consist of 6 white to off-white tablets representing PF-05221304/PF-06865571/placebo.
    - **Note:** For Visit 4 (Day -14) drug product dispensed will only consist of single-blind placebo to match PF-05221304 and PF-06865571 tablets.

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 case report form (CRF).

5.3. Subject Compliance

Compliance of single-blind placebo administration during the Run-in period will be assessed by pill count on Day 1 (Visit 6) for the purposes of inclusion into the study. Acceptable compliance will be defined as self-administration by the subjects of:

- ≥85% of the study-supplied blinded placebo taken by the subject during the Run-In period (ie, Visit 4 to Visit 6) – up to 4 single doses are permitted to be missed.

Compliance of IP administration will be assessed during the treatment phase of the study by the number of tablets returned by the subjects at Visits 7, 8, 9 and 10.

- A compliance rate of ≥80% with self-administration of the IP is expected from Day 1 (Visit 6) to Day 42 (Visit 10); investigators must closely monitor non-compliant subjects in order to enhance their adherence to the study treatment. Subjects having missed more than 2-4 doses of IP during a one week treatment period will be re-educated on the importance of compliance on their site visit. If similar non-compliance is noted on their next site visit also, the subject may be discontinued from the study, upon discussion with the Sponsor.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Blinded investigational products (5 mg PF-05221304, 100 mg PF-06865571 or their matching placebos) will be provided as white to off-white tablets for oral administration. All investigational products will be provided in blister packs and labeled according to local regulatory requirements. PF-05221304, PF-06865571, and their matching placebos for dispensation at the visits denoted in the Schedule of Activities will be packaged with blister packs containing a sufficient number of tablets to permit dosing for 14 (+2) days.

5.4.2. Preparation and Dispensing

The investigational product will be dispensed using an IRT drug management system from Visit 4 to Visit 9 [refer to Schedule of Activities]. A qualified staff member will dispense the investigational product via unique container numbers on the blister packs provided, in quantities appropriate for the study visit schedule. **Subjects should be instructed to**

maintain the IP in the blister pack(s) provided throughout the course of dosing at the labelled storage conditions and return with the dispensed blister pack(s) to the site **at each visit** starting at Visit 6 (Day 1) and through morning of Visit 10 (Day 42). The instructions for dosing will be provided to the sites and individual subjects. The number of blister packs dispensed and the number of tablets administered per dose will be identical for all randomized arms.

5.5. Administration

Subjects will be instructed to take the blinded investigational product at the same time of day, twice a day, with the morning and evening meals each day except for Day 42 dose, for which subjects would not take evening dose. In addition, subjects will be instructed to delay the self-administration of the blinded investigational product as well as other allowed, concomitant medication, if applicable, on the days of their outpatient visit to the site; on these days, these medications will be administered at the site with the morning meal.

Subjects will swallow the investigational product whole with approximately 240 mL of non-carbonated water, and will not manipulate or chew the investigational product prior to swallowing.

Subjects will be provided dosing instructions starting at Visit 4 (Day -14) to aid in remembering the correct steps to self-administer blinded investigational product.

5.6. Investigational Product Storage

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

Investigational products should be stored in their original containers and in accordance with the labels. Any storage conditions stated in the SRSD 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 investigational product 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(s) 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 investigational product(s) must be quarantined and not used until Pfizer provides permission to use the investigational product(s). It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product 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.

Site staff will instruct subjects on the proper storage requirements for take home investigational products. The site staff should refer to the Investigational Product Manual for additional guidance on storage conditions and actions to be taken when conditions are outside of the specified range.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product(s) supplies. All investigational products will be accounted for using a drug accountability form/record.

All blister packs of study drug must be returned to the investigator by the subject at every visit and at the end of the trial, except on Day 5 visit (Visit 7), when the subject will bring the un-used study drug to the site for compliance check, but will take it back with them to complete dosing for remainder of the days, until their next site visit.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product(s) (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.

For all blister packs returned to the investigator by the subject, the investigator will maintain the returned supply until destruction is authorized. Pfizer will provide instructions as to the disposition of any unused investigational product.

5.8. Concomitant Treatment(s)

Subjects in this study will be allowed to take certain concomitant medications to treat coexisting conditions such as type 2 diabetes, 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 to **not** 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(s) on Day 1 will be documented as a prior treatment. Treatments taken after the first dose of IP(s) will be documented as concomitant treatments.

5.8.1. Medications for Glycemic Control

Subjects with a diagnosis of T2DM are **permitted** to be on stable doses of 1 oral agent for glycemic control, starting at ≥8 weeks prior to Visit 1 (Screen 1) and until Visit 11 (on-site Follow-up), including (but not limited to) the following approved classes of agents:

- Sulphonylureas such as glimepiride, glipizide, glyburide;
- Dipeptidyl peptidase-4 inhibitors (DPP-4i) such as sitagliptin, saxagliptin, vildagliptin;
- Meglitinides such as repaglinide, nateglinide.

The use of the following classes of agents is **NOT** permitted starting at ≥8 weeks prior to Visit 1 and until Visit 11 (on-site Follow-up):

- Metformin;
- Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone;
- Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, pramlintide);
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors such as canagliflozin, dapagliflozin, empagliflozin.

5.8.2. 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 and throughout the study (until on-site Follow-up visit, Visit 11).

5.8.3. 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, gemfibrozil and fluvastatin are **not** permitted within **4 weeks** prior to Screen 1 and until on-site Follow-up visit;
- Bile acid sequestrants such as cholestyramine, colestipol, colesevalam;
- Fenofibrate;
- Nicotinic acid/niacin.

5.8.4. 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.

5.8.5. Prohibited Concomitant Medications

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 for administration of combination IPs, 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);
  - **Note:** short term use of potent CYP3A inhibitors (eg, ketoconazole, itraconazole) for management of fungal infections **≥ 4-weeks prior to Visit 1 (Screen 1)** is acceptable but use must be avoided post randomization.
- Sensitive breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) substrates (eg, rosuvastatin and digoxin);
- CYP2C9 substrates (eg, fluvastatin, diclofenac, celecoxib, torsemide);
- Use of chronic agents which are potent inducers of CYP3A (eg, rifampin);

- Use of CYP3A4/5 substrates with narrow therapeutic index – eg, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and terfenadine;

- Use of chronic agents which are clinically significant organic anion transporter polypeptide (OATP) inhibitors (eg, cyclosporine, gemfibrozil, rifampin).

5.9. Rescue Medication

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

6. STUDY PROCEDURES

A signed and dated Informed Consent Document (ICD) will be obtained from each subject at Visit 1 (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 Visit 1 (Screen 1).**

For the procedures described below, where multiple procedures are scheduled at the same time points relative to dosing, the following chronology of events should be adhered to as much as possible:

- ***12-lead ECG***: obtain prior to vital signs assessment, blood samples, and prior to dosing;

- ***Vital Signs (BP, pulse rate)***: obtain after 12-lead ECG collection but prior to obtaining blood samples and prior to dosing;

- ***Fasting blood samples, including pre-dose PK***: after assessment of 12-lead ECG and vital signs but prior to dosing;

- ***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 of blinded IP(s)***: must occur after any pre-dose blood sample collections.

6.1. Screening

Refer to the Schedule of Activities 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 liver fat assessment by 2nd FibroScan and by MRI-PDFF) undertaken to determine eligibility – refer to Section 4.1 and Section 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 liver fat content 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 8, Section 4.1.

For Visit 1, subjects will be instructed to arrive at the study site after at least an 8-hour, but preferably 10-hour fast (except water). For Visits 2 and 3, fasting (water allowed) for ≥4 hours is required.

Subjects will be screened **within56 days** (including 14 days of single-blind Run-In period) prior to the first dose of the blinded IP to confirm that they meet the subject selection criteria for the study. The duration between Screen 1 (Visit 1) and start of Run-In period (Visit 4) should be **at least 28 days**, but should not exceed 42 days. 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 **72 days** is exceeded. In such cases, all screening procedures must be repeated and the subject assigned a new 8-digit single subject identifier (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).

6.2. Run-in Period (Visit 4)

After the investigator has determined all eligibility criteria have been satisfied (approximately within 1 week following Visit 3), subjects will return to the site after a minimum 8-hour, but preferably 10-hour fast (except water). The single-blind Run-in period will serve to familiarize the subject with the study treatment regimen and exclude subjects who are not compliant with dosing. This visit will occur 14±2 days prior to the planned date of randomization (Visit 6, Day 1).

For all subjects, refer to the Schedule of Activities for the study procedures to be completed at the Run-in visit (Visit 4).

Following completion of the above procedures, single-blind IP will be self-administered (with meal) while witnessed by adequately trained site staff. Subjects will then be discharged from the site with enough IP to last until Day 1 (Visit 6).

6.3. Baseline MRI-PDFF (Visit 5)

Between 2 to 6 days, inclusive, prior to Visit 6 (Day 1), subjects will be instructed to report to the Imaging facility following a ≥4-hour fast, and within ±2 hours of the Visit 3 time to undergo liver fat assessment via MRI-PDFF. Subjects should self-administer single-blind IP (with meal) post-MRI-PDFF.

- **Note:** If the subjects are found to have a non-evaluable MRI-PDFF, they may have to come back to Imaging center for a single repeat assessment, preferably still within 2-4 days of the Day 1 visit (Visit 6).

- **Note:** Subjects will be informed via a phone call if they are found not to meet eligibility criteria of ≥8% liver fat. In that case, the subjects will be discontinued.

6.4. Study Period

6.4.1. Day 1 (Visit 6)

Approximately 14 days after Visit 4, subjects will return to the site after a minimum of an 8-hour, but preferably 10-hour fast.

Subjects will be asked to return IP dispensed at Visit 4 for an assessment of the pill count. Subjects must be at least 85% compliant with the placebo run-in IP in order to be randomized.

Refer to the Schedule of Activities for the study procedures to be completed prior to administration of IP on Day 1. Be sure to collect a genomic banked biospecimen for OATP genotyping. If missed, collect at the next available time point when biospecimen are being collected in conjunction with a subject visit.

Subjects who meet safety eligibility ie, ECG, vitals and weight, liver fat eligibility as determined by FibroScan (CAP™ ≥280 dB/m) and MRI-PDFF (≥8%), compliance criteria (>85% compliant) and are negative for urine drug test will be randomized to double-blind study treatment on Day 1. Sites will contact the IRT system for assignment of double-blind treatment. Double-blind IP(s) will be dispensed to subjects via IRT and self-administered. Following witnessed dosing of IP (with meal), an approximate 2-week supply of double-blind IP will be dispensed, and subjects will be discharged from the site.

6.4.2. Day 5 (Visit 7)

At 5±1 days from Visit 6, subjects will return to the study site after a minimum of an 8-hour, but preferably 10-hour fast. Subjects will bring un-used supply of IP for compliance check.

- **Note:** If subjects do not meet at least 80% compliance, subjects will be re-educated on the importance of dosing compliance.

Refer to the Schedule of Activities for the study procedures to be completed prior to administration of IP on Day 5.

Following witnessed dosing of IP (with meal), subjects will be discharged from the site with their un-used IP, to be taken for remainder of the days until their next visit (Visit 8).

6.4.3. Day 14 (Visit 8) and Day 28 (Visit 9)

At 14±2 and 28±2 days from Visit 6, subjects will return to the study site after a minimum of an 8-hour, but preferably 10-hour fast.

Refer to the Schedule of Activities for the study procedures to be completed prior to administration of IP(s) on Day 14 and on Day 28 respectively.

- **Note:** If, during compliance check it is found that a subject is <80% compliant and if this is the first time they were <80% compliant in dosing, the subject will be re-educated about importance of compliance at these visits. If this is subject's second time not meeting a minimum of 80% compliance requirement, the subject may be discontinued, after consultation with the Sponsor.

Following completion of the above procedures, double-blind IP(s) will be dispensed to subjects via IRT and self-administered (with meal). CCI [redacted]

6.4.4. Day 42 (Visit 10)

Within approximately 24 hours prior to the Day 42 visit, or on the day of the Day 42 visit, subjects will be instructed to report to the Imaging facility following a ≥4-hour fast (if the visit to the Imaging facility is 24 hours prior) or a minimum of 8-hour, but preferably 10-hour fast (if the visit to Imaging facility is on same day as site visit ie Day 42 visit) and within ±2 hours of the Visit 5 time to undergo liver fat assessment via MRI-PDFF.

Refer to the Schedule of Activities for the study procedures to be completed prior to administration of IP on Day 42.

Subjects should self-administer double-blind IP(s) (with meal) post-MRI-PDFF. If subjects perform MRI-PDFF in the morning of same day as Visit 10 site visit, they should wait for blood collections before administration of morning dose at the site. Subjects will not take evening dose on Day 42.

6.4.5. Follow-up

At ≥7 days and ≤14 days following the last dose of double-blind IP(s), subjects will return to the study site for a follow-up visit after a minimum 8-hour, but preferably 10-hour fast.

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

6.4.6. Follow-up Contact

A Follow-up contact via telephone of all subjects will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of double-blind IP(s).

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

- **Note:** this contact can be considered as on-site in order to permit follow-up of open AEs and/or abnormal laboratory tests from prior visit(s), as needed.

6.5. Subject Withdrawal/Early Termination

In this study, any subject who discontinues participation in the trial any time prior to administration of double-blind IP(s) will have no additional procedures completed. However, an early termination visit is to be considered for all subjects who were randomized and received at least 1 dose of the double-blind IP(s), and then are prematurely withdrawn from the study. Subjects should return to the site for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw but ≤14 days after last dose of double-blind IP(s). Subjects should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the assessments outlined in the Schedule of Activities. Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

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. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. 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.

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 the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. 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 all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

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.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will 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 this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will 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.

7.1. Imaging Assessments

[redacted]

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

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, and has found utility in previous trials of prospective NASH therapeutics.

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 just-in-time review of the acquired images for assessment of images being deemed evaluable, 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 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 at or prior to baseline (Visit 5) and Visit 10 (Day 42) 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.

7.1.3. 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 study sites will be informed whether a subject meets eligibility criteria or if the screening MRI-PDFF should be repeated once, as determined by the Sponsor-identified central imaging vendor. If the MRI-PDFF is non-evaluable for the 2nd time, the subject will be screen failed. For all subsequently scheduled MRI-PDFF assessments, study sites will only be informed whether the images are deemed evaluable (or not). If the MRI-PDFF images at baseline (Visit 4) and/or Visit 10 (Day 42 or before) are found non-evaluable, the assessment may be repeated once after consultation with the Sponsor. If the MRI-PDFF images are non-evaluable on single repeat also, the central imaging vendor will seek Sponsor's guidance on further steps. Sponsor may decide to have the subject re-visit the Imaging center for repeat MRI-PDFF or discontinued. If the single repeat of MRI-PDFF is to be performed for Visit 10, it has to be completed prior to Day 42 visit.

7.1.3.1. 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 MRIs images will be reviewed by the Sponsor-identified central review facility. 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 site protocols.

CCI [redacted]

7.2. Safety

7.2.1. 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. At screening only, physical exam will also include arm and waist circumference and height measurements. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

7.2.2. Body Weight and Hula-hoop Test

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

For hula-hoop test, subjects will be asked to be in the standing position with arms either to the side or vertically up above the head, feet positioned close together, and weight evenly distributed across both feet,

Using a sponsor-approved hula-hoop, an attempt will be made to slide the hoop over the subjects head and determine if the hoop can pass over the subjects' trunk and hips; Hula-hoop will be passed while the subject is at the end of a normal expiration (when lungs are at their residual capacity).

- If the hula-hoop slides easily from the head down to the feet, the subject is eligible and confirmed to fit inside the site-specific MRI machine and its respective bore size.

- If the hula-hoop cannot slide down to the feet (eg, fits snug at the waist or hips), the subject is deemed ineligible for this study.

- **Note:** as much as practically possible, the same position of the arms must be used for all MRI-PDFF assessments as used for hula-hoop test.

- **Note:** Additional details on steps for identification of the appropriate hula-hoop circumference, which depends on the individual Imaging facility's MRI machine opening (ie, bore diameter) along with bed thickness, and coils selected, will be provided in an Imaging Manual offered to the sites prior to the start of the study.

7.2.3. Blood Pressure and Pulse Rate

Blood pressure 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.

Single, seated 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 assessment at Visit 6 (Day 1) will serve as each subject's baseline;

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.

7.2.4. Electrocardiogram

In this study, assessment of cardiac conduction via 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 supine position.

- **Single, supine 12-lead ECGs** will be obtained and measurement collected prior to the first dose on Day 1 (Visit 6) will serve as each subject's baseline value.

- If the QTcF value is (a) above the threshold value (ie, is ≥60 msec from the baseline, or is ≥500 msec), or (b) if post-randomization QTcF interval is increased by ≥30 msec from the baseline **and** is >450 msec, then 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 an abnormal 12-lead ECG 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.

7.3. Clinical 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 7. Clinical Laboratory Tests

<table>
<tr><th>Hematology</th><th>Chemistry</th><th>Urinalysis</th><th>Fasting Lipid Panel</th></tr>
<tr><td rowspan="2">Hemoglobin
Hematocrit
RBC count
MCV
MCH
MCHC
Platelet count
WBC count
Total neutrophils (Abs)
Eosinophils (Abs)
Monocytes (Abs)
Basophils (Abs)
Lymphocytes (Abs)</td><td rowspan="2">BUN/urea
Creatinine [and eGFR using MDRD][a]
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[b]
Indirect bilirubin[b]
Serum cystatin C
Creatinine Kinase[c]</td><td rowspan="2">pH
Glucose (qual)
Protein (qual)
Blood (qual)
Ketones
Nitrites
Leukocyte esterase
Urobilinogen
Urine bilirubin
Microscopy[d]</td><td>Total cholesterol,
VLDL,
HDL-C,
Triglycerides
and
direct LDL-C</td></tr>
<tr><td>Other

FSH[e,g]
Urine drug test[f]
Serology (HepBsAg, HepBcAb, HCVAb, HCV RNA, HIV)[g]
Ceruloplasmin[g]
Coagulation[g] (Plasma aPTT, PT, PT/INR)
α1-antitrypsin (A1AT)[g]</td></tr>
<tr><td colspan="4">Additional Tests (Needed for Hy's Law)</td></tr>
<tr><td colspan="4">• AST, ALT (repeat)
• Total bilirubin (repeat)
• Albumin (repeat)
• Alkaline phosphatase (repeat)
• Direct bilirubin
• Indirect bilirubin
• Creatinine kinase
• GGT
• PT/INR
• Total bile acids
• Acetaminophen drug and/or protein adduct levels</td></tr>
</table>

a. Estimated glomerular filtration rate (eGFR) will be calculated using the modification of diet in renal disease (MDRD) equation. b. Direct and indirect bilirubin measured at Screen 1 and Visit 6; after initiation of investigational product, direct + indirect bilirubin are measured only when total bilirubin is > ULN. c. Test to be assessed at Screen 1 and Visit 6 only; after initiation of investigational product, this test measured only when ALT or AST is > ULN. d. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase. e. In females, only. f. Subjects may undergo random urine drug testing at the discretion of the investigator. Drug testing will be performed using dipstick and must be negative for subjects to receive IP. g. At Screening visit only.
Abbreviations: Abs = Absolute; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; aPTT = activated Partial Thromboplastin Time; BUN = Blood Urea Nitrogen; eGFR = Estimated glomerular filteration rate; HbA1c = glycosylated hemoglobin (NGSP certified method); MCH = Mean Corpuscular Hemoglobin; MCHC = Mean Corpuscular Hemoglobin Concentration; MCV = Mean Corpuscular Volume; MDRD = Modification of diet in renal disease; PT = Prothrombin Time; PT/INR = Prothrombin Time/International Normalized Ratio.

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]

7.3.1. 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 Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi)-Cystatin C equation 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:

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

Review of Cystatin C results are not required for dosing or discharge.

CCI [redacted]

CCI

[redacted]

- [redacted]
- [redacted]
- [redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

7.5. Pharmacodynamics Parameters

Blood samples for pharmacodynamics biomarker analysis - including NASH-related biomarkers, potential mechanism-related parameters, metabolic parameters, and exploratory markers of liver function - will be collected at the nominal time points specified in the Schedule of Activities.

- These samples must be processed and shipped as indicated in the study-specific laboratory manual provided to the investigator site, prior to initiation of study, to maintain sample integrity:
    - Any deviations from the 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.
    - Any scheduled collection prior to next dose of blinded investigational product, if undertaken post dose, will be captured as a protocol deviation even if results are deemed evaluable.
- Samples will be analyzed using a validated analytical method (which need not meet Good Laboratory Practice (GLP) standards, especially for these exploratory endpoints) but in all cases, the method will be in compliance with Pfizer standard operating procedures.

Refer to list of endpoints outlined in Section 2 that encompass these pharmacodynamics biomarkers. As part of understanding the effects of co-administration of the IP(s), samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes.

7.5.1. Serum for Lipid Panel

At each time point specified in the Schedule of Activities, a sufficient volume of blood (approximately 3.5 mL) will be collected into appropriately labeled tubes for analysis of total cholesterol, HDL-C, triglycerides and direct LDL-C, with the exception of lipid panel performed at Screening, which will be completed as part of Section 7.3.

Total cholesterol/HDL-C ratio and non-HDL cholesterol will be derived from the lipid panel.

CCI [redacted]

7.5.3. Apolipoprotein A1, B100 and Apolipoprotein C3

At each time point specified in Schedule of Activities, approximately 4 mL of blood will be collected to ensure sufficient serum for analysis of apolipoproteins A1, B100 and C3. These samples will be processed and shipped for analysis to the Sponsor-identified laboratory.

CCI [redacted]

CCI [redacted]

[redacted]

7.5.8. Plasma PCSK9

Blood samples (approximately 2 mL) to provide a sufficient quantity of plasma for PCSK9 analysis will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the Schedule of Activities section of the protocol. These samples will be processed and shipped for analysis to the Sponsor-identified laboratory.

7.6. Pharmacogenomics

7.6.1. Genotyping Analysis

Blood samples for genotyping may be examined to assess the impact of allelic variants of drug-metabolizing enzymes and transporters. Additionally, these samples may also be used for retrospective evaluation of additional genetic variants associated with variation in pharmacokinetics (PKs) or to explore AEs should these be observed. Samples will be retained for a period of up to 3 years after regulatory approval.

A 4 mL blood sample will be collected from each subject into a plastic dipotassium ethylenediaminetetraacetic acid (K_2EDTA) tube at times specified in the Schedule of Activities section of the protocol.

As part of further understanding the biological response to IP, samples will be used, ***at a minimum***, for OATP genotyping. In addition, the sample may be used for evaluation of other related genotyping as well as development and validation of bioanalytical methods. Any data outside of the OATP genotyping will be used for internal exploratory purposes and will not be included in the clinical study report (CSR).

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

7.7. Banked Biospecimens

Banked biospecimens will be collected from subjects for exploratory research relating to the drug response and disease/condition under study. These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each subject's privacy and confidentiality. Banked biospecimens will be assigned the subject's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimen will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived

data will be stored on password-protected computer systems. The key between the subject's ID and the subject's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also post-marketing research. Subjects may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimen will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a 2 mL blood genomic banked biospecimen Prep D1.5 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis) will be collected prior to dosing at Visit 6 to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response and disease/condition under study. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

Additional banked biospecimens to be retained for such exploratory analyses in this study include the following:

- Prep B1.5 (K_2EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis): A 2 mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

- Prep B2.5 (serum collection optimized for biomarker/proteomic/metabolomic analysis): a 2 mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

The banked biospecimens will be collected from all subjects unless prohibited by local regulations or IRB/EC decision.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document that they will not be compensated in this event.

7.7.1. Additional Research

Unless prohibited by local regulations or Institutional Review Board (IRB)/Ethics Committee (EC) decision, subjects will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Banked Biospecimens section will be used. Subjects may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

CCI [redacted]

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 6.5)

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:

Severity Assessment	
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. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. 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 liver function test (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.

8.4.3. 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.

8.4.3.1. 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.

8.4.3.2. 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.

8.4.3.3. 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.

8.4.4. 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

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 98 subjects will be randomized in a ratio of 1:2:2:2 to four treatment groups A:B:C:D, where A is the placebo group. Assuming an approximate 14% dropout rate this will ensure a minimum of 84 subjects complete the study. This sample size (12 for the placebo group and 24 for the each of monotherapy groups and the combination group) is estimated to provide >90% power to detect a difference of 30% mean reduction in whole liver fat from MRI-PDFF relative to placebo for the PF-05221304 + PF-06865571 combination using a 1-sided Type I error rate of 0.05. This randomization schema will enable detection of a smaller effect of the combo vs monotherapy than of the monotherapies vs placebo. Detecting a smaller effect requires a larger sample size and hence the sample size is increased for the active arms. With the sample size of 24 completers for each of the active arms the power to detect approximately 16% mean reduction in whole liver fat for the PF-05221304 + PF-06865571 combination relative to each monotherapy is approximately 90% using a 1-sided Type I error rate of 0.25. These calculations assume a pooled standard deviation of the log-relative change of 0.32 (based on an internal study).

9.2. Analysis of the Primary Endpoint

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

The primary endpoint will be the relative change from baseline to Day 42 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 from baseline with treatment and baseline diabetes as factors, and log-transformed baseline whole liver PDFF value as a covariate. Estimates of the mean relative changes between placebo and each active drug arm (PF-05221304 monotherapy, PF-06865571 monotherapy and PF-05221304 plus PF-06865571 combination) at Day 42, and the corresponding 90% confidence interval (CI) will be obtained from the model. Similarly, PF-05221304 plus PF-06865571 combination will be compared to each monotherapy through estimates of the mean relative change and corresponding 50% and 90% confidence intervals. 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.

9.3. Analysis of Secondary Endpoints

Secondary endpoints relate to safety and tolerability whose analyses are described in Section 9.7.

9.4. Analysis of Tertiary/Exploratory Endpoints

Percent changes from baseline in LFTs will be summarized; group medians and pairwise differences from the comparators will be presented. Log-transformed relative changes from baseline in lipid panel parameters will be analyzed separately using mixed model for repeated measures (MMRM) with treatment, study day and interaction of treatment with study day as factors, log-transformed baseline values of the dependent variable, baseline diabetes status and log-transformed baseline whole liver PDFF as covariates. CCI [redacted] If the model does not fit the data model reduction techniques might be employed; otherwise, group medians and their differences from the placebo median will be presented. Details will be provided in the SAP.

For all other pharmacodynamic endpoints/biomarkers to be included in the CSR observed values, changes from baseline and/or percent changes from baseline will be summarized descriptively at all collection time points. Details and any additional analyses will be described in the SAP.

CCI [redacted]

9.6. Analysis of Other Endpoints

Pharmacogenomic and biomarker data will be collected and retained for future analyses, but will not be analyzed for the purposes of CSR.

9.7. 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.

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.

Vital Signs Analysis

Changes from baseline in systolic blood pressure, diastolic blood pressure and pulse rate will be summarized by treatment and time. The number (%) of subjects with maximum increases from baseline will be tabulated by treatment as defined in the SAP. Numbers and percentages of subjects meeting the categorical criteria will be provided and individual values listed in the study report. No formal inferential statistics will be applied to the vital signs data.

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. QTcF will be derived using Fridericia's heart rate correction formula. The number (%) of subjects with maximum increases from baseline will be tabulated by treatment as defined in the SAP. Numbers and percentages of subjects meeting the categorical criteria will be provided and individual values listed in the study report. No formal inferential statistics will be applied to the ECG data.

9.8. Interim Analysis

If, after randomization of approximately 50% subjects of planned number of subjects, a monthly safety review reveals that the study meets one or more criteria listed in Section 3.3, an interim analysis will be performed in an un-blinded manner by a pre-specified IRC, independent from study team.CCI

Before any interim analysis is initiated, 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 IRC charter. The analysis details will be documented and approved in an interim analysis SAP or final SAP.

9.9. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct 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.

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/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 CRF is required and should be completed for each included subject. The completed original CRFs are 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 shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and 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 CRFs must be signed by the investigator or by an authorized staff member to attest that the

data contained on the CRFs are true. Any corrections to entries made in the CRFs or 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 subject chart. In these cases, data collected on the CRFs must match the data in 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 CRF, and for which the CRF will 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, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and 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. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

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 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 comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable law.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. 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 the Clinical Study Agreement and 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, the sharing of data relating to the study and possible risks associated

with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The 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 All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV) – the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subjects 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 one or both IPs (PF-05221304 and 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 trial 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 (clinical study report synopses in which any data that could be used to identify individual patients has 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

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Appendix 1. Abbreviations

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

Abbreviation	Term
A1AT	α-1-antitrypsin
Abs	absolute
ACC1/2	acetyl-CoA (coenzyme A) carboxylase 1 and 2
ACCi	acetyl-CoA (coenzyme A) carboxylase inhibitor
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
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
CDK-Epi	Chronic Kidney Disease Epidemiology Collaboration
C_{eff}	efficacious concentration
CFB	change from baseline
CI	confidence interval
CK	creatine kinase
CLr	renal clearance
C_{max}	maximum observed concentration
C_{min}	minimum concentration
CNS	central nervous system
CO2	carbon dioxide (bicarbonate)
CoA	coenzyme A
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
CV	coefficient of variation

Abbreviation	Term
CYP450	cytochrome P450
DAG	diacylglycerol
dB/m	decibels per meter
DDI	drug-drug interaction
DGAT	diacylglycerol acyltransferase
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DNL	de novo lipogenesis
DPP-4	dipeptidyl peptidase-4
DPP-IVi	dipeptidyl peptidase-IV inhibitors
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)
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EU	European Union
EudraCT	European Clinical Trials Database
FA	fatty acids
FFA	free fatty acids
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLDH	glutamate dehydrogenase
GLP	good laboratory practice
GLP-1r	glucagon-like peptide-1 receptor
hr.	hour(s)
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HDL-C	high density lipoprotein cholesterol

Abbreviation	Term
HIV	human immunodeficiency virus
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
IA	interim analysis
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
IR	immediate release
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
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
LSM	liver stiffness measure
MATE	multi-drug and toxin extrusion 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
MIST	metabolites in safety testing
MK	megakaryocytes
MMRM	mixed model for repeated measures
MR	modified release
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
N/A	not applicable
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NMN	N-methylnicotinamide

Abbreviation	Term
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
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
PGx	pharmacogenomic
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PTR	peak to trough ratio
Q8hr.	every 8 hours
Q12hr	every 12 hours
QD	quodque die (once daily)
QTc	corrected QT interval
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
Scys	serum cystatin
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
$t_{1/2}$	half-life
SSID	single subject identifier
TBili	total bilirubin
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
TG	triglycerides
Th17	T-helper 17 lineage
T_{max}	time to reach maximum concentration
Treg	regulatory T

Abbreviation	Term
TZD	thiazolidinediones
ULN	upper limit of normal
US	United States
VCTE	vibration controlled transient elastography
VLDL	very low density lipoprotein
WBC	white blood cell

Appendix 2. Strong CYP3A Inhibitors and Inducers*

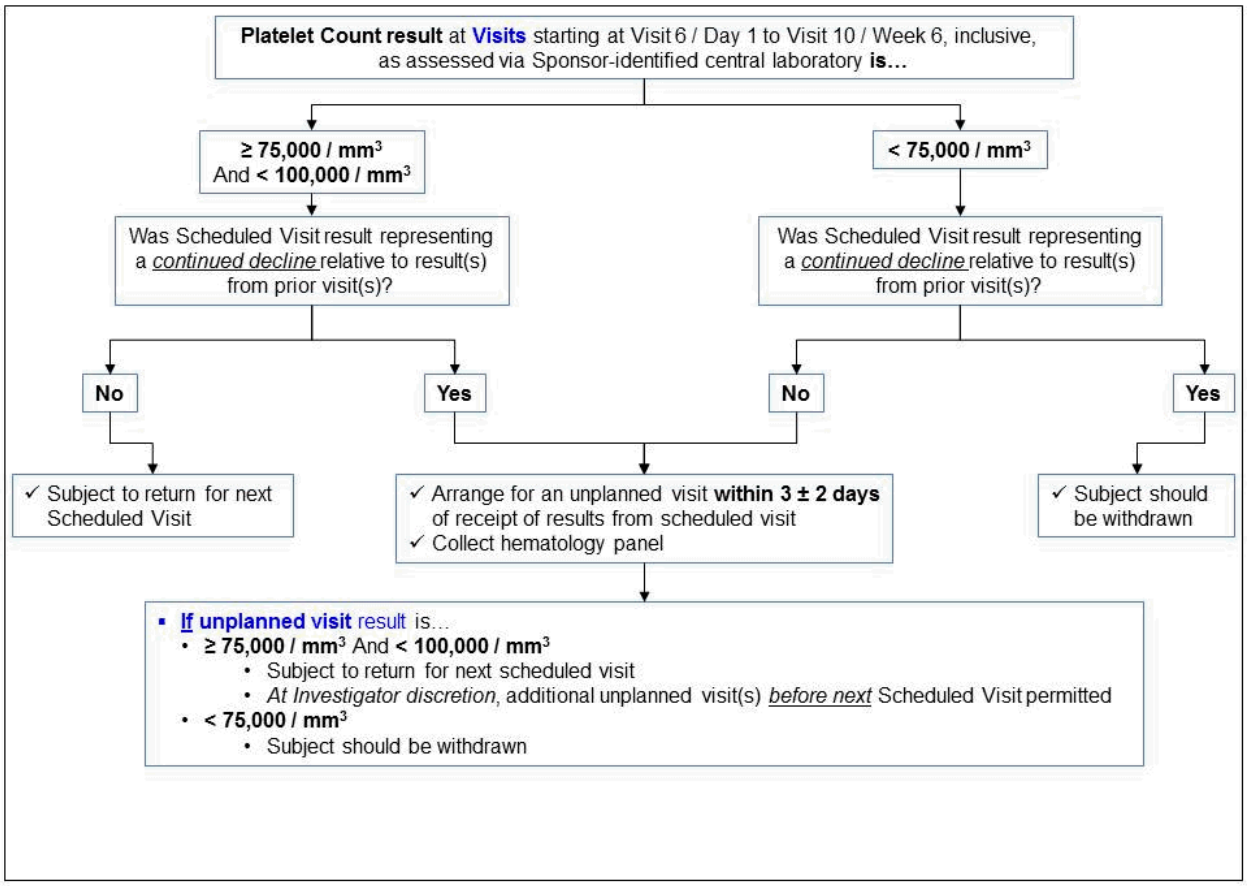
CYP 3A Inhibitors	CYP 3A Inducers
HIV antivirals	HIV antivirals
Indinavir	Nevirapine
Nelfinavir	Miscellaneous
Ritonavir	Barbiturates
Saquinavir	Carbamazepine
Boceprevir	Glucocorticoids (systemic)
Lopinavir/ritonavir	Oxcarbazepine
Amprenavir	Phenobarbital
Atazanavir	Phenytoin
Telaprevir	Rifabutin
Darunavir/ritonavir	Rifampin
Fosamprenavir	St. John's wort[2]
Tiprinavir/ritonavir	Troglitazone
Antibiotics	Nafcillin
Clarithromycin	Avasimibe[3]
Troleandomycin	Enzalutamide
Telithromycin	Mitotane
Anti-infectives	
Itraconazole	
Ketoconazole	
Posaconazole	
Voriconazole	
Miscellaneous	
Nefazodone	
Grapefruit juice1	
Conivaptan	
Idelalisib	

1. Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos).
2. The effect of St. John's wort varies widely and is preparation-dependent.
3. 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

Appendix 3. Guidance to Investigators –Management of Individual Subjects With Decrease in Platelet Count



Appendix 4. Guidance to Investigators –Management of Individual Subjects With Elevation in Fasting Serum Triglycerides