A PHASE 2A, 2-PART, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY PLACEBO-CONTROLLED, PARALLEL-GROUP (SPONSOR OPEN) STUDY TO ASSESS PHARMACODYNAMICS AND SAFETY OF PF-06865571 (DGAT2I) COADMINISTERED WITH PF-05221304 (ACCI) IN ADULT PARTICIPANTS WITH PRESUMED NONALCOHOLIC STEATOHEPATITIS (NASH)

Study Intervention Number:	PF-06865571 (DGAT2i) PF-05221304 (ACCi)
Study Intervention Name:	N/A
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Protocol Number:	C3711005
Phase:	2a

Short Title: Parallel-Group Study of PD and Safety of DGAT2i and ACCi Coadministered in Participants with Sponsor-defined Presumed NASH

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	27 March 2020	N/A

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In this document, the two investigational products are referred to as DGAT2i (for PF-06865571) and ACCi (for PF-05221304).

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: Parallel-Group Study of PD and Safety of DGAT2i and ACCi Coadministered in Participants with Sponsor-Defined Presumed NASH.

Rationale: The current study is to evaluate the effect of coadministration of a range of doses of DGAT2i with 1 (and potentially 2) doses of ACCi, on the primary pharmacology (effect on liver steatosis) and evaluate the ability of a range of doses of DGAT2i to mitigate ACCi-induced elevations in serum triglycerides. This is the first clinical study specifically designed to identify the lowest dose of DGAT2i which, when coadministered with ACCi, results in reduction in hepatic steatosis while mitigating the identified adverse reaction (ie, elevation in serum triglycerides) observed with administration of ACCi alone.

This study has a 2-part design with sequential conduct of Part 1 and Part 2 with each part conducted in distinct/separate cohorts of participants. While the overall study design, objectives/endpoints, eligibility criteria for both parts are envisioned to remain identical, data from Part 1 will be used to determine whether to conduct Part 2. Observed data from Part 1 will guide the selection of doses and dosing regimens (ie, QD vs BID) of DGAT2i + ACCi coadministration evaluated in optional Part 2.

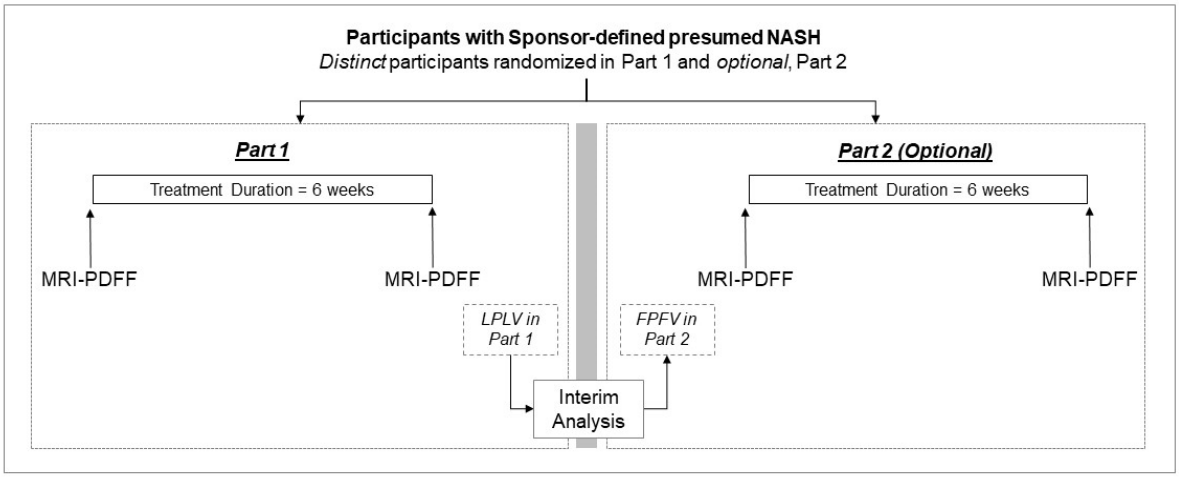
Objectives, Estimands, and Endpoints: The primary, secondary, and key tertiary/exploratory endpoints of focus in **Part 1** and *optional* **Part 2** of this study include:

Objectives	Estimands	Endpoints
Primary:		
To evaluate **effect on liver fat**, determined by MRI-PDFF, of a range of DGAT2i doses coadministered with a fixed dose of ACCi compared to placebo in participants with presumed NASH.	Estimand 1: This estimand is intended to provide a population level estimate of the mean treatment effect (DGAT2i + ACCi relative to placebo) on a continuous endpoint at Week 6 for all randomized/evaluable participants (see details in Section 9.1.1).	Percent change from baseline in liver fat as assessed via MRI-PDFF, at Week 6.
Secondary:		
To evaluate effect on fasting serum **triglyceride levels** of a range of DGAT2i doses coadministered with a fixed dose of ACCi compared to placebo in participants with presumed NASH	Estimand 2: This estimand is intended to provide a population level estimate of the mean treatment effect (DGAT2i + ACCi relative to placebo) on a continuous endpoint, over time, for all randomized/evaluable participants (see details in Section 9.1.1).	Percent change from baseline in fasting serum triglyceride levels over time.

Objectives	Estimands	Endpoints
To assess **safety and tolerability** with a range of DGAT2i doses coadministered with fixed dose of ACCi compared to placebo in participants with presumed NASH.	No estimand is defined for safety and tolerability endpoints.	Proportion of participants with TEAEs and clinically-significant, abnormal clinical laboratory tests, vital signs, and 12-lead ECGs.
Tertiary/Exploratory:		
To evaluate effect on **liver fat** determined by quantitative ultrasound (FibroScan®) of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH.	This Endpoint will be analyzed using Estimand 1.	Percent change from baseline in liver fat at Week 6, as assessed by CAP™ via FibroScan®.
To evaluate effect on **liver fat** determined by quantitative ultrasound (Acuson Sequoia®) of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH.	This Endpoint will be analyzed using Estimand 1.	Percent change from baseline in liver fat at Week 6, as assessed by UDFF™ via Acuson Sequoia®.

For ***all*** endpoints, baseline is defined as the evaluable result closest but ***prior*** to dosing on Day 1.

Overall Design: This is a multicenter, 2-part, sequentially conducted, randomized, double-blind, double-dummy, placebo-controlled, parallel-group evaluation of DGAT2i + ACCi summarized below.



Number of Participants

In Part 1, approximately 90 participants (18 per group) with Sponsor-defined presumed NASH, will be randomly assigned to the study intervention to ensure approximately 75 evaluable participants (15 per group) offer evaluable data.

In Part 2, it is envisioned that number of participants on each *active* dose of DGAT2i + ACCi or placebo *may* be adjusted. Those assigned to placebo *may* be reduced, given the intent to pool data from all participants receiving placebo when summarizing end-of-study results. The doses of DGAT2i in Part 2 will not exceed 300 mg BID or 300 mg QD. The doses of ACCi will not exceed 20 mg/day (administered BID or QD to mirror dosing of DGAT2i). A maximum of 4 active doses (plus placebo) will be evaluated in Part 2; furthermore, the total number of participants will not exceed 90 (with no more than approximately 27 participants per each *active* dose).

Intervention Groups and Duration: In Part 1, study interventions planned to be administered up to 6-weeks are summarized below.

Group	Each Dose Group in Part 1		
	DGAT2i dose	**ACCi dose**	**DGAT2i:ACCi ratio**
A	0 (placebo) BID	0 (placebo) BID	0: 0
B	25 mg BID	10 mg BID	2.5: 1
C	100 mg BID	10 mg BID	10: 1
D	300 mg QD*	20 mg QD*	15: 1
E	300 mg BID	10 mg BID	30: 1

*To maintain double-blind, double-dummy design across all groups, this group will receive placebo as their evening dose

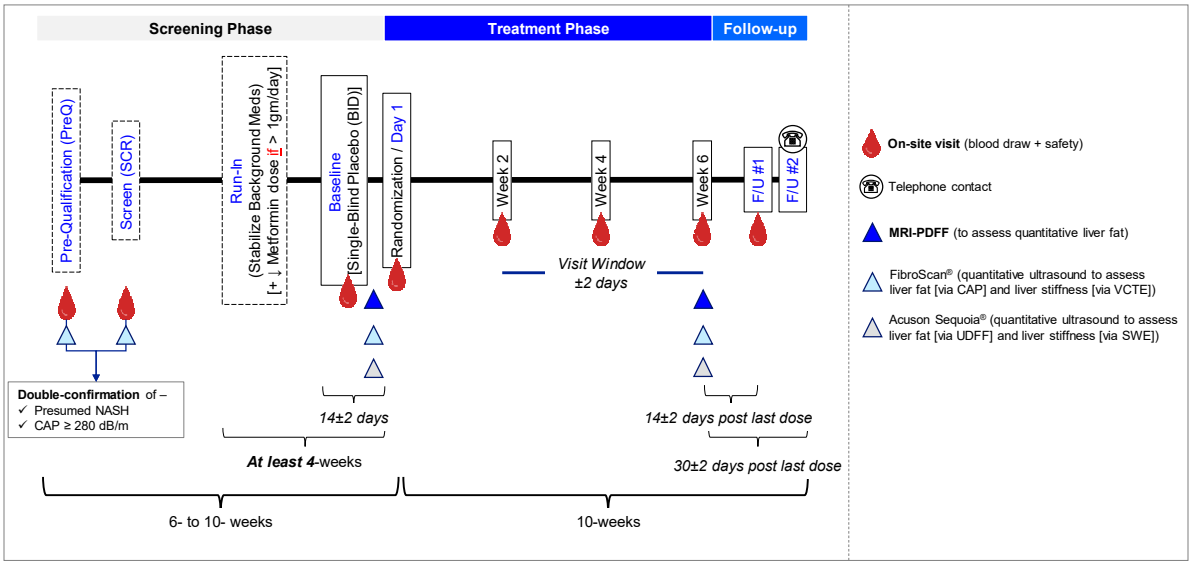
In Part 2, if conducted, the doses, as well as dosing regimens (ie, QD vs BID) evaluated for DGAT2i + ACCi will be guided by observed data in Part 1.

Data Monitoring Committee or Other Independent Oversight Committee: An independent Internal Review Committee (IRC) will undertake periodic unblinded review of the safety data while the study is on-going.

Statistical Methods: Natural log-transformed relative change from baseline in fasting liver fat values determined using MRI-PDFF, CAP™ via FibroScan®, and UDFF™ via Acuson Sequoia® for DGAT2i + ACCi relative to placebo at Week 6 for all randomized/evaluable participants will be analyzed using an ANCOVA with treatment as fixed effect and baseline as covariate. Natural log-transformed relative changes from baseline in fasting serum triglycerides for DGAT2i + ACCi relative to placebo will be analyzed using mixed model repeated measures (MMRM) analysis including treatment, time, and treatment-by-time interaction as fixed effects, baseline as a covariate effect and participant as a random effect. All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations.

1.2. Schema

The detailed set-up of the study is summarized below with identical design for Part 1 and *optional* Part 2 planned.



1.3. Schedule of Activities

The 2 Schedule of Activities (SoA) tables provide an overview of the protocol visits and procedures. Refer to the Section 8 of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The SoA tables are identical for Part 1 and *optional* Part 2.

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

Table 1. Procedures for Part 1 and *Optional* Part 2

Visit Identifier	PreQ	SCR	Run-In	Baseline	Treatment Phase [All, except Imaging procedures, before morning dose of blinded study intervention]				Follow-up		Study D/C
Weeks[a] Relative to Dosing on Day 1			-4	-2	0 Day 1	2	4	6	8	10[b]	
Visit #	0	1	2	3	4	5	6	7	8	9	
Informed consent & demography	x	x									
(Update) Medical & Medication Information	x	x	x	x	x	x	x	x	x		x
Liver fat and stiffness (via FibroScan®)[c,d]	x	x		x				x			
Liver fat via MRI-PDFF[c,d]				x				x			
Liver fat and stiffness (via Acuson Sequoia®)[c,d]				x				x			
Physical Exam (PE)[e]	x	x		x	x	x	x	x	x		x
Assess alcohol intake (AUDIT questionnaire)	x	x			x			x			
Assess correct use of contraception, where applicable			x	x	x	x	x	x	x		x[f]
Counseling on diet/exercise guidelines			x		x						
Open-ended inquiry for adverse events (AEs)	x	x	x	x	x	x	x	x	x	x	x
Single supine 12-lead ECG	x	x			x			x	x		x
Single seated vitals (BP & pulse rate) and body weight	x	x			x			x	x		x
Registration of visit in study (via IRT)	x	x	x	x	x	x	x	x	x	x	x
Onsite administration of study intervention, with meal[g]				x	x	x	x	x			
Dispensation (via IRT) of study intervention				x	x	x	x				
Compliance check of ***returned*** study intervention[h]					x[g]	x	x	x			x

a. Defined **relative to Day 1** with permitted ±2-day window for each visit starting at Baseline/Visit 3; for example: Week -2 = 14 (±2) days before Day 1; Week 4 = 28 (±2) days post Day 1.

b. Telephone contact can be switched to on-site visits for follow-up of AEs and/or abnormal laboratory tests; Week 10 visit at ≥28- and ≤32 days post last dose (Day 30±2 days).

c. Procedure performed following ≥4-hour fast (except water), as part of on-site visit ***or*** separate visit(s) to Imaging/Radiology facility; attempts to be made to perform Week 6 assessment within ±2-hour window of time of 1st assessment (PreQ for FibroScan® and Baseline/Visit 3 for MRI-PDFF and Acuson Sequoia®).

d. Baseline assessments performed at or after Visit 3 and before dosing on Day 1/Visit 4; Week 6 performed ≤2 days post last dose of blinded study intervention.

e. Complete PE at PreQ and SCR and includes arm circumference (at PreQ only) and height and waist circumference (at both PreQ and SCR); otherwise, brief PEfor open adverse events (AEs)/abnormal laboratory tests, at investigator discretion.

f. WOCBP participants to be reminded to continue required contraception until at least 28 days post-last dose.

g. Onsite dosing should be performed with single-blind, double-dummy placebo dispensed at Baseline/Visit 3 through 1 day *prior* to Day 1; double-blind, double-dummy study intervention starting on Day 1/Visit 4.

h. Performed at on-site visits with Day 1/Day 4 reflecting compliance with single-blind, double-dummy placebo; at subsequent visits, reflects compliance with double-blind, double-dummy study intervention.

Table 2. Blood and Urine Collection in Part 1 and *Optional* Part 2

Visit Identifier	PreQ	SCR	Run-In	Baseline	Treatment Phase [All procedures before **morning dose** of blinded study intervention, ***except*** post-dose PK samples]				Follow-up		Study D/C
Weeks[a] Relative to Dosing on Day 1			-4	-2	0 Day 1	2	4	6	8	10[b]	
Visit #	0	1	2	3	4	5	6	7	8	9	
Blood Collection (following fast of ≥8 hours)			*No blood or urine collection*								
Serum FSH (females only), serology (HBsAg, HCVAb [and if positive, reflex HCV RNA], HIV), α1-antitrypsin, ceruloplasmin	x[c]	x[c]									
% CDT	x[c]	x[c]			x			x			
Hematology, Chemistry (including Cystatin-C), Coagulation (aPTT, PT, INR)	x[c]	x[c]		x[c]	x	x	x	x	x	x[d]	x
Pregnancy (***all*** females)	x[c]	x[c]		x[c]	x	x	x	x	x	x[d]	x
Triglycerides, *direct* LDL-C, HDL-C, total cholesterol	x[c]	x[c]		x[c]	x	x	x	x	x	x[d]	x
HbA1C, Plasma Glucose	x[c]	x[c]		x[c]	x	x	x	x	x	x[d]	x
Direct VLDL, Serum apolipoproteins: ApoA1, $ApoB_{total}$, $ApoB_{100}$, $ApoB_{48}$, ApoC3, ApoE; Pro-C3, Pro-C6, and hs-CRP				x	x	x	x	x	x		
Plasma PCSK9, Adiponectin, CK18-M30, CK18-M65, Plasma Insulin				x	x	x	x	x	x		
Predose PK - DGAT2i and ACCi[e]					x	x	x	x			
Post dose PK - DGAT2i and ACCi[f]					x	x	x				
Pre-specified PGx *and* Biobanked Prep D1 (DNA)					x						
Biobanked Prep B1.5 (plasma) and Prep B2.5 (serum)					x		x	x			
spot urine collection for –											
Urine drug test	x[c]	x[c]		x[c]							
Urinalysis (and microscopy when appropriate)	x[c]	x[c]		x[c]	x	x	x	x	x	x[d]	x
On-site pregnancy test (WOCBP only)					x[c]	x[c]	x[c]	x	x	x[d]	x

a. Defined **relative to Day 1** with permitted ±2 day window for each visit starting at Baseline/Visit 3; for example: Week -2 = 14 (±2) days before Day 1/Visit 4; Week 4 = 28 (±2) days post Day 1/Visit 4.

b. Telephone contact can be switched to on-site visits for follow-up of AEs and/or abnormal laboratory tests; Week 10 visit at ≥28 and ≤32 days post last dose (Day 30±2 days).

c. Test results to be reviewed by medically qualified site staff and deemed acceptable before progression to next visit; for example: PreQ results must be reviewed prior to conduct of SCR.

d. Collections to occur only if visit is an on-site visit; collections to be skipped if visit is via telephone contact.

e. In addition to blood collection, date and time of 2 ***most recent doses*** should be noted in a dosing diary prior to each scheduled on-site visit plus date/time of study intervention taken on-site must be captured in the eCRF.

f. Collection to occur between 0.5-1 hour post dose on Day 1; between 2-3 hours post dose at Week 2; and between 4-8 hours post dose at Week 4.

2. INTRODUCTION

The current study is to evaluate the effect of coadministration of a range of doses of DGAT2i with 1 (and potentially 2) doses of ACCi, on the primary pharmacology (effect on liver steatosis) and evaluate the ability of a range of doses of DGAT2i to mitigate ACCi-induced elevations in serum triglycerides. This is the first clinical study specifically designed to identify the lowest dose of DGAT2i which, when coadministered with ACCi, results in reduction in hepatic steatosis while mitigating the identified adverse reaction (ie, elevation in serum triglycerides) observed with administration of ACCi alone.

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

ACC is a biotin carboxylase that catalyzes the ATP dependent condensation of acetyl-CoA and carbonate to form malonyl-CoA.[4] Inhibition of ACC stimulates fatty acid oxidation, suppresses hepatic *de novo* lipogenesis (DNL), and reduces steatosis in animal models and in humans.[5] ACCi has been shown to decrease hepatic DNL (in healthy participants following 14-days of dosing), reduce liver steatosis (in participants with NAFLD), as well as reduce markers of liver inflammation (ALT, AST) and markers of apoptotic activity (CK18-M30 and CK18-M65), in participants with Sponsor-defined presumed NASH following 16 weeks of dosing. However, these potentially beneficial effects, in participants with NAFLD/presumed NASH, were accompanied with marked elevations in serum triglycerides and other lipid parameters which prohibit administration of ACCi alone.

In nonclinical models of NAFLD/NASH, coadministration of DGAT2i + ACCi has been shown to be more efficacious at lowering hepatic steatosis, and reducing inflammation and fibrosis endpoints, than either DGAT2i or ACCi alone. In addition, coadministration of DGAT2i + ACCi fully reversed the increases in circulating fasting serum triglycerides observed with ACCi alone – overcoming the known mechanistic consequence of hepatic ACCi thought to be a result of sterol regulatory element binding protein (SREBP) activation. Clinically, the effect of ACCi alone on fasting serum triglycerides has been shown to be mitigated following 6-week of dosing of DGAT2i + ACCi in participants with NAFLD while maintaining significant reduction in hepatic steatosis.

2.1. Study Rationale

The current study is an extension of a recently concluded study (C3711001) assessing placebo, DGAT2i alone (300 mg BID), ACCi alone (15 mg BID), and coadministration of DGAT2i + ACCi for a treatment duration of up to 6 weeks in participants with NAFLD. In Study C3711001, a placebo-adjusted LS mean reduction in liver fat of ≥35% was observed in all active groups. In addition, on average, the increases in fasting serum triglyceride levels observed with ACCi alone were mitigated by coadministration with DGAT2i. It is anticipated that via coadministration of DGAT2i + ACCi, hepatic lipid metabolism will be modulated in distinct and complementary ways, potentially resulting in greater efficacy than DGAT2i administered alone. However, whether the effect on primary pharmacology can be maintained along with mitigation of ACCi-induced elevation in fasting serum triglycerides via lower doses of DGAT2i as well as QD administration of both agents remains to be tested and forms the purpose of the current study. While Study C3711001 population included participants with NAFLD, population in the current study is proposed as ***presumed NASH***, as defined by the Sponsor as participants meeting **all** of following via ***double-confirmation*** between the PreQ and SCR visits:

- Liver fat as assessed via quantitative ultrasound parameter CAP™ of ≥280 dB/m, assessed using FibroScan®;
- Liver stiffness as assessed via quantitative ultrasound parameter VCTE™ of ≥7 kPa, assessed using FibroScan®;
- Presence of ***at least 2*** of the 5 concomitant medical conditions which are associated with NAFLD – refer to criterion # 3 in Section 5; ***and***
- ALT > ULN (and ≤5 x ULN).

In the current study, a 2-part design with sequential conduct of Part 1 and Part 2 with each part conducted in distinct/separate cohorts of participants is proposed. While the overall study design, objectives/endpoints, eligibility criteria for both parts are envisioned to remain identical, data from Part 1 will be used to determine whether to conduct Part 2. Observed data from Part 1 will guide the selection of doses and dosing regimens (ie, QD vs BID) of DGAT2i + ACCi coadministration evaluated in Part 2.

2.2. Background

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 HCC. NASH is diagnosed clinically by liver biopsy demonstrating steatosis, inflammation, and cytological ballooning of liver hepatocytes, often with varying degrees of fibrosis. NASH progresses with increasing severity of fibrosis, with cirrhosis developing in a subset of participants[6] and a common complication of cirrhosis being HCC.[7] NASH is a subset of NAFLD (defined as presence of ≥5% hepatic steatosis in the absence of other liver disease etiologies) that is associated with increased all-cause mortality, cirrhosis and end stage liver disease, increased

cardiovascular mortality, and increased incidence of both liver related and non-liver related cancers.[6]

In a meta-analysis, the global prevalence of NAFLD was estimated at 25%, with the prevalence of NASH in the subset with biopsy-proven NAFLD assessed at 59%.[8] The majority of the population with NAFLD has simple steatosis which has, in general, a benign clinical course. A proportion of participants with NAFLD progress to having hepatocellular ballooning and lobular inflammation, taking close to a decade to progress from 1 stage to the next and 30-40 years to develop cirrhosis; however, a smaller subset of participants progress very rapidly (within 10 years) to liver cirrhosis from NAFLD.[8] 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 participants with NASH is significantly different than in those with NAFLD. The pooled liver-specific and overall mortality incidence rate estimates among those with NAFLD were calculated at 0.8 and 15.4, respectively, per 1,000 person-years. In contrast, amongst the population with NASH, the incidence rate estimates were 11.8 (liver-specific) and 25.6 (overall) mortality.[8]

Elevated rates of hepatic DNL have been reported to be a distinctive characteristic of NAFLD.[9] Clinically, those with elevated liver fat showed a more than 3-fold increase in the rate of hepatic DNL relative to participants with normal liver fat, but no differences between the groups were detected in adipose FFA flux or in production of VLDL from FFAs. Furthermore, 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 investigated as an early intervention strategy.

2.2.1. Clinical Overview

As of *January 2020*, safety and efficacy of DGAT2i alone or when coadministered with ACCi in the target patient population (ie, those with biopsy-confirmed NASH with liver fibrosis stage 2 or 3) has not been evaluated although clinical activity and effectiveness of DGAT2i alone and when coadministered with ACCi has been assessed in participants with NAFLD with dosing up to 6 weeks.

Across the clinical studies completed/concluded with DGAT2i alone (n=6 studies), ACCi alone (n=6 studies) and DGAT2i + ACCi (n=2 studies), 736 *unique* participants have been randomized, with 120 (16%) exposed to placebo, 161 (22%) exposed to DGAT2i alone, 407 (55%) exposed to ACCi alone, 44 (6%) exposed to DGAT2i + ACCi, and 4 exposed to metformin alone in the DGAT2i-Metformin DDI study. DGAT2i alone has been evaluated as single oral doses up to 1500 mg, repeated doses up to 1800 mg/day (administered Q8H) for up to 14 days, and repeated doses of 600 mg/day (administered Q12H) for up to 6 weeks. ACCi alone has been administered at single, oral doses up to 240 mg, repeated (≤14-days) doses up to 200 mg/day (administered QD and Q12H), and repeated (≤16 weeks) doses up to 50 mg/day (administered QD). DGAT2i + ACCi has been evaluated at a single coadministered dose level of 300 mg BID (DGAT2i) + 15 mg BID (ACCi).

DGAT2i alone *or* as DGAT2i + ACCi has been evaluated in six Phase 1 studies in healthy adults (with 132 participants randomized) and two studies (1 Phase 1 and 1 Phase 2a) in participants with NAFLD (with 148 participants randomized). ACCi alone has been evaluated in five Phase 1 studies in adults (with 151 participants randomized) and one Phase 2a, dose-ranging study in participants with NAFLD (n=305 randomized including 68% with Sponsor-defined presumed NASH).

Administration of DGAT2i alone has been found to be well tolerated with an acceptable safety profile with no special safety concerns identified. Upon repeated administration of DGAT2i, across the 20-fold dose range evaluated (ie, 90 to 1800 mg/day), TEAEs reported in ≥7 (3%) participants across all groups evaluated were headache (11%), diarrhea (6%), fatigue (5%), pruritus (4%), abdominal pain (3%), and nausea (3%). Upon repeated administration of ACCi, across a 100-fold dose range evaluated (ie, 2 to 200 mg/day), the all-causality TEAEs reported in ≥1.5% of participants were headache (9%), diarrhea (7%), hypertriglyceridemia (6%), and nausea (5%).

Given DGAT2i is a dose-dependent inhibitor of the transporters OCT2/MATE in kidney, as expected, increases in serum creatinine without a change in renal function (as assessed via eGFR determined using Cystatin-C) was noted. Dosing with ACCi alone resulted in 2 identified adverse drug reactions – namely, increases in fasting serum triglycerides, and decrease in platelet count, with reversal in 1 to 2 weeks post discontinuation of ACCi alone observed, refer to Section 2.3.1. Based on review of pooled TEAEs, 12-lead ECG data, blood pressure data, and laboratory data, coadministration of DGAT2i + ACCi has been shown to not result in worsening of the safety profile relative to either agent administered alone. However, coadministration of DGAT2i + ACCi at the doses tested in Study C3711001 (300 mg BID + 15 mg BID) was shown to mitigate the ACCi-induced elevations in fasting serum triglycerides, ApoC3, and non-HDL. There were no clinically significant adverse effects noted in other safety-related assessments such as blood pressure, and cardiac conduction intervals [assessed on 12-lead ECGs] with DGAT2i, ACCi, and DGAT2i + ACCi.

Upon repeated dosing of DGAT2i with standard meals, C_{max} was achieved at 1.5-3 hours post dose. Steady-state plasma concentrations were achieved by Day 4, and the mean terminal $t_{½}$ ranged from 3.3-6.9 hours. Dosing in the fasted state resulted in lower exposures (ie, AUC_{inf} 39% lower and C_{max} 34% lower than when a 1000 mg DGAT2i dose was administered with a standard meal). Following oral dosing of ACCi with a high-fat/high-caloric meal, C_{max} was achieved at 3-5 hours post-dose, and the mean terminal $t_{½}$ ranged from 13-18 hours. There was no clinically relevant effect on exposure with dosing of ACCi in the fasted versus fed state. Coadministration of DGAT2i (300 mg BID) and ACCi (15 mg BID) resulted in a slight decrease in the systemic exposure of ACCi with adjusted geometric mean (90% CI) of 12% (2-20%) lower (for C_{max}) and 19% (12-26%) lower (for AUC_{tau}). There was no marked effect on the systemic exposure of DGAT2i, when coadministered with ACCi, with adjusted geometric mean 8% higher (for C_{max} and AUC_{tau}).

2.2.2. Nonclinical Overview

DGAT2i and ACCi have each individually been evaluated in a comprehensive nonclinical safety package that included rat and cynomolgus monkey toxicity studies up to 6 and 9 months duration, respectively, and in reproductive and developmental toxicology studies in rats and rabbits, and together (ie, DGAT2i + ACCi) in combination toxicity studies in monkeys up to 13 weeks in duration.

For DGAT2i alone, no adverse findings were identified in rats or cynomolgus monkeys. At the NOAEL in the 9-month study in cynomolgus monkeys, exposure margins relative to a highest clinical dose of 300 mg BID were 4.6x and 7.3x the unbound human C_{max} and AUC_{24}, respectively. At the NOAEL in the 6-month study in rats, exposure margins were 1.6/6.8x (male/female) and 1.8/7.7x (male/female) the unbound human C_{max} and AUC_{24}, respectively.

For ACCi alone, all adverse findings were related to the inhibition of fatty acid biosynthesis, due to the pharmacology of ACCi, and were observed as changes in the lung, skin, nonglandular stomach, or Meibomian glands. At the NOAEL in the 9-month study in cynomolgus monkeys, exposure margins relative to the highest clinical dose of 20 mg/day (with most conservative QD dosing and margins for C_{max}) were 110x and 51x, the predicted human unbound C_{max} and AUC_{24}, respectively, and at the NOAEL in the 6-month study in rats exposure margins were 65x and 18x the predicted unbound human C_{max} and AUC_{24}, respectively.

DGAT2i + ACCi were evaluated in cynomolgus monkey toxicity studies up to 13 weeks duration. All findings were attributed to ACCi and no new adverse findings were identified in monkeys administered DGAT2i + ACCi. Exposure margins in the 13-week study in cynomolgus monkeys relative to a DGAT2i clinical dose of 300 mg BID were 2.9x and 4.5x, the predicted human unbound C_{max} and AUC_{24}, respectively, and exposure margins relative to a ACCi clinical dose of 20 mg/day (with most conservative QD dosing and margins for C_{max}) were 141x and 49x the predicted unbound human C_{max} and AUC_{24}, respectively.

For review of EFD findings in studies completed with DGAT2i and separately with ACCi alone, refer to Section 2.3.1.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of DGAT2i alone, DGAT2i + ACCi, and ACCi alone may be found in the IB for DGAT2i and *separately* for ACCi, which will serve as the 2 SRSDs for this study.

A high level summary of potential risks as well as benefits are offered in Section 2.3.1 and Section 2.3.2.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention – DGAT2i (as part of DGAT2i + ACCi)		
Drug-drug interactions resulting in change in DGAT2i exposure.	*In vitro* data indicate DGAT2i having low hepatic clearance and multi-pathway metabolism with: • CYP3A – major (f_m 0.68); • CYP2B6 – minor (f_m 0.16); • CYP2C19 – minor (f_m 0.16).	Study excludes participant on potent inhibitors or inducers of CYP3A – refer to Section 6.5.
Study Intervention – DGAT2i (as part of DGAT2i + ACCi)		
Drug-drug interactions resulting in change in exposure of background/concomitant medications.	Clinical data indicate that DGAT2i at 300 mg BID can increase plasma metformin exposure by 2-fold.	Starting at Run-In (ie, approximately *4* weeks before randomization), participants on metformin dose >1 gm/day must agree to metformin dose decreased by 1/3 or 1/2 with up-titration post randomization based on FPG results – refer to Section 6.5.1 and Appendix 10.9.
	In vitro data indicate DGAT2i at 300 mg BID to be a: • Potent BCRP inhibitor; • Inhibitor of P-gp; • Inhibitor of CYP2C9.	Use of specific medications that are substrates for BCRP, P-gp and/or CYP2C9 will be excluded (or restricted) – refer to Section 6.5.
Food effect resulting in change in DGAT2i exposure.	Clinical data indicate that DGAT2i exposures are lower in fasted state than in fed state.	Investigational products will be taken with a meal.
Fetal skeletal variations as a result of transient developmental delay.	• In embryo-fetal development toxicity study ***in rats***, lower fetal body weight and skeletal anomalies observed at all doses with NOAEL for this developmental toxicity not identified. • In embryo-fetal development toxicity study ***in rabbits***, no developmental toxicity observed.	• Risk of fetal toxicity communicated through the DGAT2i IB (Jan-2020). • Enrollment of women of childbearing potential restricted to those using effective contraception – refer to Section 5.4.1 and Appendix 10.4. • In males who are sexually active with a female partner of childbearing potential, use of barrier methods ***not*** required/mandated given safety margins >100-fold – refer to Section 5.4.1 and Appendix 10.4.
Study Intervention – ACCi (as part of DGAT2i + ACCi)		
Increase in serum triglycerides.	• Identified adverse reaction with inhibition of hepatic ACC; observed upon repeated dosing of ACCi alone in healthy participants and in those with NAFLD/presumed NASH. • Magnitude of elevation in	• Administration of ACCi alone not planned. • Study requires fasting serum triglyceride ≤400 mg/dL (4.5 mmol/L) at multiple timepoints prior to randomization. • Given that elevations occurred early

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	NAFLD/presumed NASH observed to be approximately 2-fold higher than in healthy participants – based on exposure: response population PK.	post initiation of dosing, visits post randomization, initially, scheduled to be every 2 weeks. • Management of isolated and double-confirmed elevations in fasting serum triglycerides planned – refer to Appendix 10.10. • Reversal in fasting serum triglycerides expected (and observed) upon discontinuation of ACCi.
Decrease in platelet count.	Identified adverse reaction with ACCi; observed upon repeated dosing of ACCi alone in healthy participants and those with NAFLD/presumed NASH.	• Study requires platelet count to be ≥LLN at multiple timepoints prior to randomization. • Management of isolated and double-confirmed declines in platelet count planned – refer to Appendix 10.11. • Reversal in platelet count expected (and observed) upon discontinuation of ACCi.
Drug-drug interactions resulting in change in ACCi exposure.	*In vitro* data indicate ACCi cleared via OATP-mediated hepatic uptake and metabolism (predominantly via 3A4).	Study excludes participant on potent inhibitors of OATP and potent inhibitors and inducers of CYP3A4 – refer to Section 6.5.
Fetal external malformation and skeletal variations and malformations.	• In EFD study ***in rats***, ACCi at highest dose, resulted in higher incidence of fetal skeletal variations (ie, structural changes to ribs, skull, sternebrae and vertebrae) plus delay in ossification of skull and sternebrae. • In EFD study ***in rabbits***, ACCi at highest dose produced fetal skeletal malformations including absent skull bones, malformed ribs, and malformed vertebrae; ACCi delayed ossification of thoracic vertebrae and produced variations in development of skull, ribs, and vertebrae.	• Risk of fetal toxicity communicated through the ACCi IB (Dec-2019). • Enrollment of women of childbearing potential restricted to those using effective contraception – refer to Section 5.4.1 and Appendix 10.4. • As a measure of caution, serum pregnancy testing to be undertaken in all females. • In males who are sexually active with a female partner of childbearing potential, use of barrier methods *not* required/mandated given safety margins >100-fold – refer to Section 5.4.1 and Appendix 10.4.
Study Procedures		
Conduct of different imaging assessments of liver fat during study (ie, quantitative ultrasound-based FibroScan® and Acuson Sequoia® as well as	Procedures are relatively safe; potential risk for non-evaluable images include: • Too much motion, for example, due to increased anxiety, claustrophobia. • Ferric implants/devices,	• Permitting pre-procedure use of anxiolytics to manage anxiety (in case of MRI-PDFF). • Excluding participants if they have contraindications for MRI, or quantitative ultrasound based assessments (FibroScan® and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
MRI-PDFF).	paramagnetic objects within/on body, ferric-containing tattoos in area of interest (abdomen, chest, arms). • Minimum duration of a priori fast ***not*** followed.	Acuson Sequoia®). • Clear communication via ICD of preparation for each visit *including* duration of fast before procedures/visits.
Other Factors Potentially Impacting Study Results		
Distinction of drug-induced liver injury from disease-related baseline elevations in LFTs.	Population eligible likely to have elevated ALT and AST (though not Alkaline phosphatase, total bilirubin).	• Study requires *double-confirmation* of stable ALT, AST, alkaline phosphatase (ie, ≤50% variability[10]) plus total bilirubin ≤ ULN ***before*** proceeding with screening/ baseline.

Coadministration of DGAT2i + ACCi, based on completed toxicity studies in rats and monkeys, as well as completed clinical studies, does not afford any additional adverse findings above and beyond those identified with administration of ACCi alone. Thus, in the current study, any adverse clinical impact of the above findings are expected to be minimized through: (1) the proposed frequent visits to site to permit close oversight of participants' safety via medical monitoring of a range of clinical assessments including safety-related laboratory tests, 12-lead ECGs, vitals, assessment of AEs; (2) inclusion of provisions for management of glycemic control (refer to Appendix 10.9) and the 2 identified adverse reactions ie, increases in fasting serum triglycerides (refer to Appendix 10.10) and reduction in platelet count (refer to Appendix 10.11); **and** (3) institution of an independent, IRC (refer to Section 9.5) to undertake unblinded review of the safety data while the study is on-going.

2.3.2. Benefit Assessment

For the participants in this study, close monitoring of their medical condition and safety will occur as outlined in this protocol. In Part 1, 4 out every 5 participants randomized will receive DGAT2i + ACCi and therefore, may potentially derive short-term benefit from the primary pharmacology, namely, reduction in hepatic steatosis. Those randomized to placebo (1 in every 5 participants) are not expected to obtain any specific benefit, beyond close monitoring of their medical condition and overall close follow-up of their safety. All participants will receive general, standard-of-care guidance/counseling regarding the overall benefits of diet/exercise. In Part 2, if conducted, similar benefits are likely inferred to participants who will be randomized.

2.3.3. Overall Benefit/Risk Conclusion

Additional details about the known and expected benefits and risks and reasonably expected adverse events with administration of DGAT2i alone, DGAT2i + ACCi, and ACCi alone may be found in the IB for DGAT2i and *separately* for ACCi, which serve as the 2 SRSDs for this study. Considering all available clinical and nonclinical data, the benefit:risk profile of DGAT2i and DGAT2i+ACCi supports continued clinical development as outlined in this protocol.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

The planned identical objectives, estimands, and endpoints for Part 1 and optional Part 2 of this study are summarized below.

Objectives	Estimands	Endpoints
Primary:		
To evaluate **effect on liver fat**, determined by MRI-PDFF, of a range of DGAT2i doses coadministered with a fixed dose of ACCi compared to placebo in participants with presumed NASH.	Estimand 1: This estimand is intended to provide a population level estimate of the mean treatment effect (DGAT2i + ACCi relative to placebo) on a continuous endpoint at Week 6 for all randomized/evaluable participants (see details in Section 9.1.1).	Percent change from baseline in liver fat as assessed via MRI-PDFF, at Week 6.
Secondary:		
To evaluate effect on fasting serum **triglyceride levels** of a range of DGAT2i doses coadministered with a fixed dose of ACCi compared to placebo in participants with presumed NASH.	Estimand 2: This estimand is intended to provide a population level estimate of the mean treatment effect (DGAT2i + ACCi relative to placebo) on a continuous endpoint, over time for all randomized/evaluable participants (see details in Section 9.1.1).	Percent change from baseline in fasting serum triglyceride levels over time.
To assess **safety and tolerability** with a range of DGAT2i doses coadministered with fixed dose of ACCi compared to placebo in participants with presumed NASH.	No estimand is defined for safety and tolerability endpoints.	Proportion of participants with treatment-emergent adverse events (TEAEs) and clinically significant, abnormal clinical laboratory tests, vital signs, and 12-lead ECGs.
Tertiary/Exploratory:		
To evaluate effect on **liver fat** determined by quantitative ultrasound (FibroScan®) of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH.	This endpoint will be analyzed using Estimand 1.	Percent change from baseline in liver fat at Week 6, as assessed by CAP™ via FibroScan®.
To evaluate effect on **liver fat** determined by quantitative ultrasound (Acuson Sequoia®) of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH.	This endpoint will be analyzed using Estimand 1.	Percent change from baseline in liver fat at Week 6, as assessed by UDFF™ via Acuson Sequoia®.

For ***all*** endpoints, baseline is defined as the evaluable result closest but ***prior*** to dosing on Day 1.

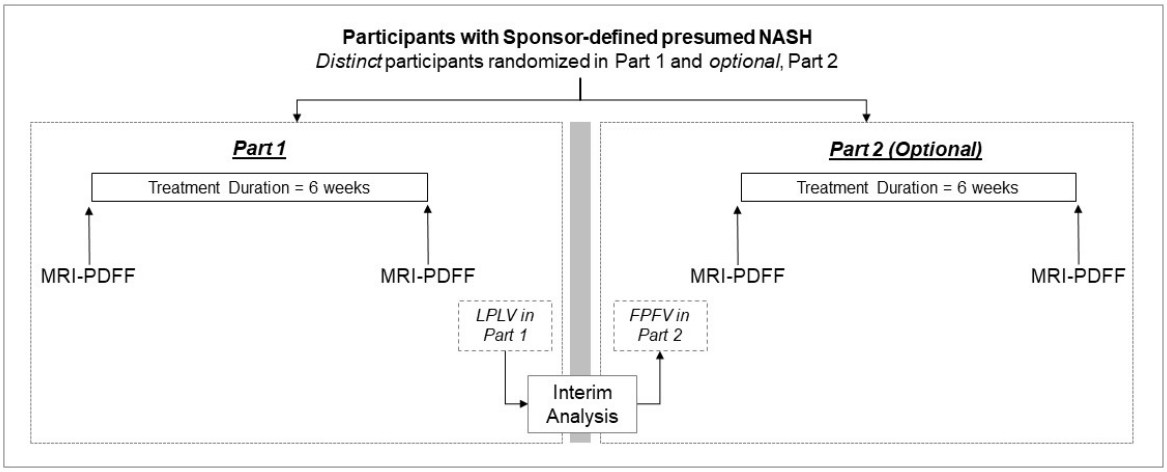
Additional tertiary/exploratory objectives and endpoints are listed in Section 9.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, 2-part, sequentially conducted, randomized, double-blind, double-dummy, placebo-controlled, parallel-group evaluation of DGAT2i + ACCi as summarized in Figure 1.

Figure 1. Overall Study Design



4.1.1. Part 1

Study interventions planned are summarized in Table 3.

Table 3. Planned Dosing Groups in Part 1 of Study C3711005

Group	DGAT2i Dose	ACCi Dose	DGAT2i:ACCi Ratio
A	0 (placebo) BID	0 (placebo) BID	0: 0
B	25 mg BID	10 mg BID	2.5: 1
C	100 mg BID	10 mg BID	10: 1
D	300 mg QD*	20 mg QD*	15: 1
E	300 mg BID	10 mg BID	30: 1

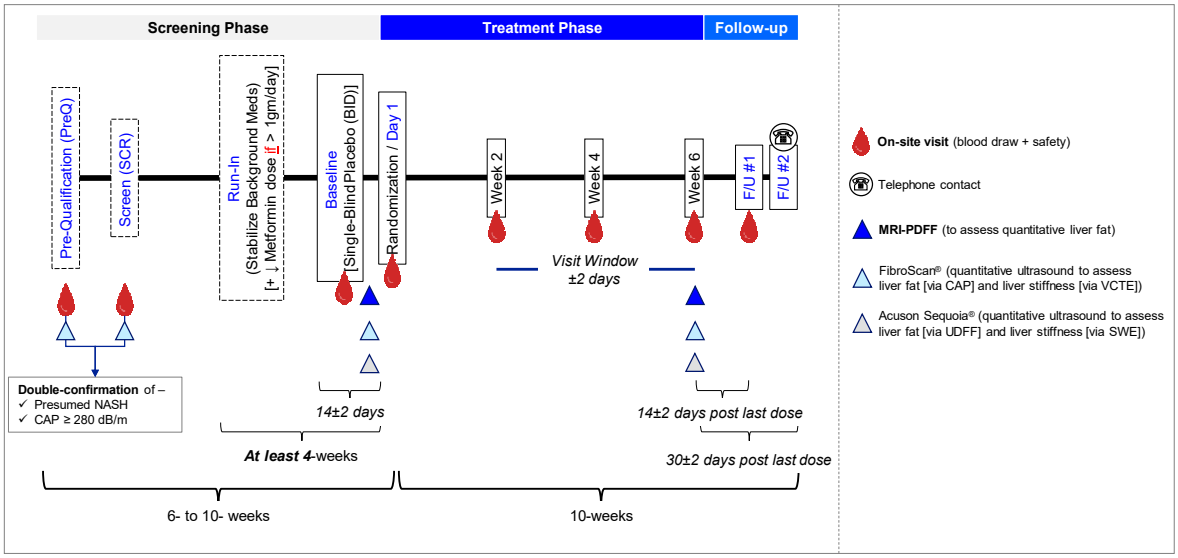
* In order to maintain double-blind, double-dummy design across all groups, this group will receive placebo as their evening dose.

Dosing in all groups will be accommodated via administration of 3 tablets per dose, and 6 tablets per day. The use of blister packed supplies is planned to minimize dosing errors and to enhance compliance, refer to Table 4 in Section 6.1 for details.

Determination of eligibility will occur via a sequential, 2-step process starting with Prequalification visit (PreQ). Participants identified to be eligible at PreQ will transition to the main study, starting with Screening (SCR) visit. The double-confirmation (at PreQ and SCR) will permit progression of only a selected subset of participants confirmed to meet Sponsor-defined presumed NASH criteria (along with other eligibility criteria) to the

Run-In/Visit 2. At the Run-In/Visit 2, stabilization of concomitant medicines may occur, as needed/appropriate (refer to Section 6.5). All eligible participants must complete the Run-In/Visit 2, followed by Baseline/Visit 3. On Day 1/Visit 4, participants who meet the randomization criteria (Section 5.3) will be assigned to receive 1 of 5 double-blind, double-dummy regimens (refer to Table 3) for a duration of up to 6 weeks, refer to Figure 2.

Figure 2. Study Design for Part 1 and *Optional* Part 2



Approximately 90 participants (18 per group) with Sponsor-defined presumed NASH will be randomly assigned to the study intervention to ensure approximately 75 evaluable participants (15 per group) offer evaluable data.

4.1.2. Optional Part 2

Part 2 may be initiated after *unblinded* review of the data from Part 1 by selected members of the Sponsors' study team (the investigators/site staff as well as site-facing study team members will remain blinded), refer to Section 9.5. This interim analysis will include review of primary endpoint data (effect on hepatic steatosis as assessed via MRI-PDFF) as well as overall safety/tolerability including degree of mitigation of ACCi-induced effect on fasting serum triglycerides achieved across the range of DGAT2i:ACCi dose ratios evaluated. Guided by these data, Part 2 may enroll up to 5 dose groups (including placebo) with intent to evaluate additional permutations of doses of both DGAT2i and ACCi administered BID or QD. However, the doses of DGAT2i in Part 2 will not exceed 300 mg BID or 300 mg QD and the dose(s) of ACCi will not exceed 20 mg/day (administered BID or QD to mirror dosing of DGAT2i). A maximum of 4 active doses (plus placebo) will be evaluated in Part 2; furthermore, the total number of participants will not exceed 90 (with no more than approximately 27 participants per each *active* dose).

Following aspects are envisioned to remain identical between Part 1 and *optional* Part 2:

- Eligibility (refer to Section 5.1 and Section 5.2) and randomization (refer to Section 5.3) criteria;
- Schedule of activities including assessment of standard safety/tolerability (via vitals, 12-lead ECG, laboratory tests), refer to SoA – Table 1 and SoA - Table 2;
- Overall study design including duration of dosing, refer to Figure 2.

In order to enable accumulation of safety experience in the clinical program, minimize potential carry over effect, as well as control selection bias, participants randomized and dosed double-blind, double-dummy study intervention in Part 1 of this study are not eligible for Part 2.

4.2. Scientific Rationale for Study Design

Reduction in hepatic steatosis with DGAT2i alone, ACCi alone, and DGAT2i + ACCi have been shown in participants with NAFLD with dosing of the intervention for as little as 2 weeks (DGAT2i alone), 6 weeks (DGAT2i alone plus DGAT2i + ACCi), and up to 16 weeks (with ACCi alone). The current study is an extension of a recently concluded study (C3711001) assessing placebo, DGAT2i alone (300 mg BID), ACCi alone (15 mg BID), and coadministration of DGAT2i + ACCi, for a treatment duration of 6 weeks in participants with NAFLD. The current study is designed to find the lowest dose of DGAT2i which will mitigate ACCi-induced elevations in fasting serum triglyceride, while maintaining effectiveness (as assessed via reduction in hepatic steatosis). Data from Part 1 will dictate conduct of, the doses, and the dosing regimens (ie, QD vs BID) of DGAT2i + ACCi, potentially evaluated in Part 2.

In this study, 2 separate informed consents will be obtained: the first consent is limited to PreQ visit activities only; and the second consent is for the main study only (from Screening through participant completion/Early Termination) in those deemed to meet eligibility criteria based on non-invasive procedures completed at PreQ. Between the PreQ and SCR visits, many of the non-invasive procedures and clinical laboratory tests assessed are identical. This is motivated by the intent to confirm that the population progressed to Run-In/Visit 2 is consistently characterized as Sponsor-defined presumed NASH. As a measure of additional diligence and as an attempt to remove variability due to laboratory-to-laboratory differences, the clinical laboratory tests assessed at PreQ and SCR are proposed to be analyzed by the Sponsor-identified central laboratory. The assessments to narrow the population ultimately progressed to Run-In/Visit 2 consist of ***double-confirmation*** between assessment at PreQ and SCR of: (a) blood-based markers of liver function (ie, ALT, AST, alkaline phosphatase, total bilirubin) and ensuring participants have stable results (defined by ≤50% variability in ALT/AST/alkaline phosphatase[10] plus total bilirubin ≤ ULN, unless Gilbert's syndrome); ***and*** (b) a constellation of clinical and liver imaging characteristics which are highly suggestive of a NASH diagnosis (in the absence of a liver biopsy) referred to as Sponsor-defined presumed NASH.

ACCi alone is not planned for evaluation in this study given the previously described undesirable changes in fasting serum triglycerides encountered with liver-targeted ACC inhibitors and their potential implications for long term cardiometabolic health.

In this study, based on a combination of thorough medical history (including assessment of ethanol intake and administration of the *interview-version* of the AUDIT-10 -item questionnaire[11]), and clinical laboratory tests (ie, %CDT), medically qualified site-staff will be required to rule out alcohol based as well as and/or other causes of hepatic steatosis/inflammation/fibrosis[12], and ensure that the population enrolled is confirmed, as best as possible, to have Sponsor-defined presumed NASH. These assessments (AUDIT and %CDT) will be re-assessed prior to randomization and at end of dosing to confirm that while in the study alcohol intake remained in moderation. Participants with previously confirmed genetic polymorphisms, for example, PNPLA3 carriers, are eligible given that these polymorphisms are known to modify/increase risk for steatohepatitis but do not by themselves cause steatohepatitis.

An explicit intent in this study is to exclude those with severe hepatic impairment (eg., ascites, hepatic encephalopathy, cirrhosis, and HCC) and severe renal impairment (ie, eGFR using CKD-EPI-Cystatin-C[13] ≤30 mL/min) via specific eligibility criteria (refer to Section 5.1 and Section 5.2). This is in line with the clinical data to date showing ≤3-fold increase in plasma exposure in severe hepatic impairment as defined by Child-Pugh classification for ACCi and preliminary, partial PK data from 2 (of planned 6) participants with mild, 3 (of planned 6) participants with moderate plus 5 (of planned 6) participants with severe hepatic impairment in the on-going Phase 1 Study (C2541009) with DGAT2i in participants with varying degrees of hepatic impairment compared to historical data in healthy participants in Study C2541001; as well as renal elimination confirmed to represent <2% of unchanged drug for both DGAT2i and ACCi. The major clearance mechanism for DGAT2i and ACCi is predicted to be multi-pathway. Thus, the inclusion/exclusion criteria have been defined to help limit pharmacokinetic variability while also capturing a population that is characteristic of the intended target population. Plasma samples (both pre- and post-dose) to permit population-pharmacokinetic analysis will be collected to further examine the effect of demographics on pharmacokinetic variability and to explore the relationship of PK to PD endpoints.

The current study also undertakes assessment for potential improvement of safety-related, metabolic markers and selected biomarkers. The parameters include markers of liver function tests (ALT, AST, Alkaline phosphatase, GGT, total bilirubin), NASH-related biomarkers[14] (CK18-M30 and CK18-M65, markers of apoptotic activity; ProC3, a marker of fibrinogenesis; ProC6, a marker of fibrinolysis), glycemic parameters (HbA1C, FPG, FPI, HOMA-IR, adiponectin), and fasting lipid parameters/markers of target engagement (total cholesterol, triglycerides, direct LDL-C, HDL-C, direct VLDL, apolipoprotein A1, B_{total}, B_{100}, B_{48}, C3, and E *plus* PCSK9, hs-CRP). In addition, banking of plasma (Prep B1.5) and serum (Prep B2.5) collections are planned to enable retrospective analysis of (yet to be identified) sensitive/specific biomarkers of disease diagnosis, and/or treatment effect.

For the assessment of liver fat (via MRI-PDFF, CAP™ using FibroScan®, and UDFF™ via Acuson Sequoia®) and liver stiffness (via VCTE™ using FibroScan®, and SWE™ via Acuson Sequoia®), participants will be required to fast (water permitted) for ≥**4 hours** given the ability of food to potentially impact these results. As an additional measure to limit variability, attempts will be made to standardize the nominal time of these assessments. The clock time of day when these assessments are made should fall within a practical window (±2 hours) relative to clock time at the time of 1st assessment in this study (ie, PreQ for FibroScan®; Baseline for MRI-PDFF and Acuson Sequoia®).

In this study, while exploratory comparison of observed effect on liver fat is planned, comparing MRI-PDFF, CAP™ using FibroScan®, and UDFF™ via Acuson Sequoia®, a comparison of treatment effect on liver stiffness (via VCTE™ using FibroScan®, and SWE™ via Acuson Sequoia®), is not planned especially considering the short duration of dosing (ie, 6 weeks). However, 1 of the exploratory objectives included in this study (refer to Table 5) is comparison of the performance of the two quantitative ultrasound technologies (FibroScan® and Acuson Sequoia®) in their ability to assess liver stiffness (via VCTE™ and SWE™), respectively.

In this study, measures to ensure participant safety include: (a) frequent (every 2 weeks), outpatient visits up to Week 6/Visit 7, with provisions for unplanned visits for follow-up of AEs; (b) off study intervention observation via an on-site follow-up visit 14±2 days post-last dose and a telephone contact ≥28 and ≤32 days post-last dose; (c) *as much as practically doable*, the use of same-day shipment of safety-related blood/urine samples to Sponsor-identified central laboratory with rapid turn-around of safety-related results; (d) standardized management of metformin dose as well as overall glycemic control in those with T2DM ± managed via metformin (Appendix 10.9); (e) standardization of *blinded* management of the two identified adverse drug reactions with administration of ACCi - namely increases in fasting serum triglycerides (refer to Appendix 10.10) and reductions in platelet count (refer to Appendix 10.11); (f) establishment of IRC (refer to Section 9.5 to undertake *unblinded* review of safety data while the study is on-going; and (g) monthly *blinded* review of safety by the Sponsor's clinical team members to assess for potential trigger for additional unblinded review(s) of cumulating safety data while the study is on-going.

Plasma exposure of ACCi following a high fat/high caloric breakfast was similar relative to administration of ACCi following an overnight fast; however, plasma exposure of DGAT2i is reduced by 39% (AUC_{inf}) and 35% (C_{max}) when administered following an overnight fast versus with standard meal. Therefore, administration of the study interventions in this study will be requested to occur with the morning (and evening) meals – given the importance of regular meals to the standard of care diet counselling for the planned population.

For all participants deemed eligible after SCR visit, ***transition to Run-In/Visit 2 is mandatory*** for stabilizing background medications (including simply compliance) and accompanying monitoring parameters in order to minimize placebo response post randomization. In addition, a fixed, single-blind, 2 week baseline period from

Baseline/Visit 3 to one day prior to Day 1/Visit 4 is included in this study with the explicit purpose of familiarizing the participants with the dosing instructions for the study intervention (refer to SoA -Table 1), and to exclude participants who are *not* compliant with the single-blind placebo prior to randomization in an attempt to minimize medications errors post randomization.

4.2.1. Participants of Child-bearing Potential

Human reproductive safety data are *not* available for DGAT2i + ACCi.

In the completed, nonclinical embryo-fetal developmental studies with DGAT2i alone and ACCi alone (and hence DGAT2i + ACCi in this study) findings have been noted, refer to Section 2.3.1. Therefore, the **use of a highly effective method of contraception is required** by females of childbearing potential, refer to Section 5.4.1 and Appendix 10.4 for additional details.

The potential risk of exposure, via ejaculate, to DGAT2i + ACCi in a female sexual partner of childbearing potential of a male participant in this study is low. As such, use of barrier methods of contraception is *not* required/mandated in the male participants. The calculated safety margin is >100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of >100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[15]

4.2.2. Rationale for Banked Biospecimen Collections

Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention. Comparing the DNA, RNA, protein, and metabolite variation patterns of participants who respond well and those who respond poorly to treatment may help to better define the most appropriate group of participants in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the BBS make it possible to better understand the investigational product's 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 also can be used in research for NAFLD/NASH. Refer to Section 8.8.1 for additional details.

Providing these biospecimens is a required study activity for study sites and participants, unless prohibited by local regulations or EC decision.

4.3. Justification for Dose

4.3.1. Part 1

In Part 1, a range of doses of DGAT2i will be coadministered with fixed dose of ACCi (20 mg/day). Doses selected (refer to Table 3) were based on the observed effect on liver fat following 2 weeks of dosing with DGAT2i in Study C2541005, 6 weeks of dosing of DGAT2i alone, ACCi alone, and coadministration in Study C3711001, as well as 16 weeks of dosing with ACCi alone in Study C1171002.

In Study C3711001, administration of DGAT2i 300 mg BID and ACCi 15 mg BID alone and when coadministered over 6 weeks in participants with NAFLD, a placebo-adjusted LS mean reduction in liver fat of ≥35% was observed in all groups. In addition, on average, fasting serum triglyceride increases observed with ACCi alone were mitigated by coadministration with DGAT2i. In the current study, coadministration of DGAT2i + ACCi (at a ratio of 20:1) was selected as the highest dose; it contains the same DGAT2i dose assessed in Study C3711001 (DGAT2i 300 mg BID + ACCi 15 mg BID; at a ratio of 30:1) though a slightly lower ACCi dose (10 mg BID) is proposed in the current study acknowledging that while mitigation of ACCi-induced effect on fasting serum triglycerides with coadministration of DGAT2i was seen, this response had an upper 90% CI of an increase of 28% in placebo-adjusted change from baseline for DGAT2i + ACCi, in Study C3711001.

The lower doses of 50 mg/day and 200 mg/day of DGAT2i, administered BID (ie, 25 mg BID and 100 mg BID), in this study are proposed in order to assess the dose-response for mitigation of ACCi-induced elevations in fasting serum triglycerides, as well as to assess the effect of these coadministered doses on liver steatosis. Given that DGAT2i decreases PCSK9 with an ED_{50} of 7 mg BID and that PCSK9 is a marker of SREBP activity (mechanism postulated to be responsible for the DGAT2i-mediated mitigation of ACCi-induced elevations in fasting serum triglycerides), it is possible that doses significantly lower than 300 mg BID may mitigate ACCi-mediated lipid changes. Spacing of the DGAT2i doses by 3-4 fold allow for covering a 12-fold range of DGAT2i doses (ie, 50 to 600, mg/day).

In addition to a range of BID doses, a QD group is included where 300 mg DGAT2i will be coadministered with 20 mg ACCi. As 300 mg dose of DGAT2i represents the highest currently feasible QD dose, the purpose of this group is to assess the effect of a QD dosing regimen on hepatic steatosis as well as the potential to evaluate whether DGAT2i dose to mitigate ACCi-mediated elevations in fasting serum triglycerides can be administered QD. Depending on the observed profile with this QD dosing regimen in Part 1, additional dose ranging with QD doses may be considered in Part 2 of this study.

The DGAT2i and ACCi doses selected have been demonstrated to be safe and well-tolerated in previous clinical studies and are supported by the safety margins from the nonclinical, chronic toxicity studies completed in rats and monkeys for each of the agents alone and up to 13-week combination toxicity studies completed in monkeys. In the current study, the highest DGAT2i dose (300 mg BID) and ACCi dose (10 mg BID) proposed are 3 times (for DGAT2i) and 10 times (for ACCi) lower than the highest repeated dose evaluated for each

agent in previous clinical studies (refer to Section 2.2.1) as well as afford adequate safety margins compared to completed nonclinical chronic toxicity studies (refer to Section 2.2.2).

The overall selection of doses of DGAT2i and ACCi were also influenced by the aim to evaluate the study objectives using the tablet strengths available (ie, 25, 50, and 150 mg for DGAT2i; 10 mg and 20 mg for ACCi) as efficiently as possible. As proposed, the dose-range planned in Part 1 will necessitate each participant to self-administer 3 tablets/dose, twice daily, in order to maintain the double-blind, double-dummy design of the study. To aid compliance by the participants, study intervention will be packaged and dispensed as blister cards (not bottles) with each card permitting 7 days of dosing, refer to Section 6.1.

4.3.2. Optional Part 2

The planned dose range for DGAT2i + ACCi (both BID and QD) in Part 1 are envisioned to permit selection of dose(s) to be evaluated in Part 2.

Based on observed data in Part 1 (refer to Section 9.5), doses and/or dosing regimen selected in Part 2 will be in accordance with the following considerations:

- *Total daily doses* of DGAT2i, administered QD, will range from 25 mg (lowest) to 300 mg (highest);
- *Total daily doses* of DGAT2i, administered BID, will range from 50 mg (lowest) to 600 mg (highest);
- With DGAT2i doses projected to be sufficiently separated based on plasma exposure;
- Coadministered with ACCi dose of 10 mg/day ***or*** 20 mg/day with frequency mirroring DGAT2i dosing regimen – BID or QD;
- DGAT2i + ACCi dose(s) evaluated in Part 1 may be repeated to permit better characterization of effectiveness of DGAT2i to mitigate ACCi-induced elevation in fasting serum triglycerides;
- And each dose will be limited to ≤4 tablets (ie, up to 8 tablets per day) with drug packaged and dispensed as blister cards (not bottles) with each card permitting 7 days of dosing.

While data from Part 1 (via an interim analysis) will be used to guide dose groups evaluated in Part 2, data for any dose groups repeated in Part 1 and Part 2 (at a minimum placebo), will be pooled for purposes of reporting in the clinical study report.

4.4. End of Study Definition

End of the study is defined as the date of conduct of the very last 2nd Follow-up visit in a participant randomized into this trial, globally.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants between the ages of 18 and 75 years, inclusive, at PreQ *and* SCR.

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

Type of Participant and Disease Characteristics:

2. At PreQ *and* SCR, meet the following criteria, based on assessment via FibroScan®, with a single repeat permitted, ***on a separate day***, to assess eligibility, if needed, at ***each*** of these 2 visits:

    - CAP™ ≥280 dB/m;

    - VCTE™ ≥7.0 kPa.

3. At PreQ *and* SCR, meet ≥**2** of the following criteria [*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]:

    - Fasting Plasma Glucose (FPG) ≥100 mg/dL (5.6 mmol/L), or on pharmacological agents *with explicit purpose* of improving glycemic control (refer to Section 6.5.1 for acceptable versus prohibited medications);

    - 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 6.5.2 for acceptable versus prohibited medications);

- Fasting serum triglyceride ≥150 mg/dL (1.7 mmol/L), or on pharmacological agents *with explicit purpose* to decrease serum triglycerides (refer to Section 6.5.2 for acceptable versus prohibited medications);

- Seated blood pressure (BP) ≥130 / 85 mm Hg, or on pharmacological agents *with explicit purpose* for BP control (refer to Section 6.5.3 for acceptable versus prohibited medications);

- Waist circumference ≥40 inches (102 cm) for males and ≥35 inches (89 cm) for females.

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

Weight:

5. BMI ≥25 kg/m^2 ***with*** upper limit of 40 kg/m^2 (inclusive) at PreQ and SCR with a single repeat assessment of body weight and/or BMI permitted *on a different day* to assess eligibility, if needed, at ***each*** of these 2 visits.

6. Body weight must be stable (not vary by ≥5% for at least 12 weeks before SCR), as reported by the participant.

Informed Consent:

7. Participants are capable of giving signed informed consent as described in Appendix 10.1 which includes compliance with the requirements and restrictions listed in the ICDs and in this protocol at PreQ and SCR.

    - For participants who qualify based on PreQ procedures, at SCR, evidence of a ***separate*** personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the main study, is required.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Current significant alcohol consumption at PreQ ***and*** SCR defined as any ***one*** of these parameters – with a single repeat assessment of laboratory-related parameters permitted using the Sponsor-identified central laboratory, to assess eligibility, if needed, at ***each*** of these 2 visits:

- >14 drinks/week (men) and >7 drinks/week (women) where 1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor;
- % CDT (carbohydrate deficient transferrin) ≥1.5x ULN;
- Total score of ≥8 on the AUDIT questionnaire.

2. Evidence of other causes of liver disease at PreQ ***or*** SCR, with a single repeat assessment of laboratory-related parameters permitted using the Sponsor-identified central laboratory, to assess eligibility, if needed, at ***each*** of these 2 visits – including:
   - Alcoholic steatohepatitis;
   - Compensated and decompensated cirrhosis;
   - Active viral hepatitis B – defined by presence of HBsAg;
   - Active viral hepatitis C – defined as presence of HCVAb;
   - HIV infection defined as presence of HIV antibody;
   - Hepatocellular carcinoma or other types of liver cancer;
   - Wilson's disease, defined as ceruloplasmin level <0.1 g/L;
   - A1AT deficiency, defined as A1AT level <LLN;
   - Upper gastrointestinal bleed due to esophageal varices, liver transplant, or current MELD-Na score[16] >12;
   - Evidence of *presumptive* cirrhosis based on assessments performed as part of this study.
3. History of pancreatitis *or* T1DM, at PreQ.
4. Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, ileal resection), at PreQ:
   - Participants who have undergone cholecystectomy and/or appendectomy are eligible for this study so long as the surgery occurred >6 months prior to PreQ.
5. Diagnosis of T2DM which requires management with >3 ***oral*** medications within 12 weeks prior to SCR ***or*** management with excluded agents for glycemic control, refer to Section 6.5.1.

6. Dyslipidemia which requires management with >3 lipid-modifying agents within 12 weeks prior to SCR ***or*** use of excluded agents for lipid management:

    - In addition, specific restrictions need to be satisfied **at SCR** in order to progress to randomization;

        - Those on gemfibrozil will need to agree to be switched to another agent once deemed eligible (at initiation of Run-In) and for duration of study;

        - Those on statins will be permitted based on review of the total daily dose, refer to Section 6.5.2.

7. At PreQ ***or*** SCR, those with severe hypertension defined as seated systolic BP ≥180 mmHg and diastolic BP ≥105 mm Hg with a single repeat permitted, if needed, to assess eligibility at ***each*** of these 2 visits; **and/or** managed with >3 agents to control BP within 12 weeks prior to SCR (refer to Section 6.5.3 for acceptable medications):

    - BP must be assessed using a blood pressure cuff size available at individual sites and compatible with the arm circumference of the participant, refer to Section 8.2.4;

    - Participants with seated BP ≥160/100 mmHg at PreQ ***or*** SCR to use the Run-In period to revise/adjust medications to improve BP control;

        - In those with hypertension, BP must be well-controlled in order to progress with randomization, refer to Section 5.3.

8. Cardiovascular event within 12 months prior to PreQ:

    - A history of myocardial infarction, stroke, transient ischemic attack or revascularization procedure to prevent any of these events;

    - A history of congestive heart failure (NYHA class III or IV) or unstable angina.

9. Recent (within 5 years of PreQ) systemically administered treatments for malignancy including (but not limited to) the use of chemotherapy, radiotherapy, ***or*** immunotherapy.

    - ***Or*** any other active malignancy (within 3 years of PreQ), except for adequately treated basal cell or squamous cell skin cancer, or carcinoma *in situ*.

10. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

11. At SCR, on any prohibited concomitant medication(s) or those unwilling/unable to switch to permitted concomitant medication(s), refer to Section 6.5.5.

Prior/Concurrent Clinical Study Experience:

12. Known prior participation in a trial involving DGAT2i ***or*** ACCi (ie, randomized and received at least 1 dose of study intervention, including placebo).

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

Diagnostic Assessments:

14. Results as reported by Sponsor-identified central laboratory, at PreQ *and* SCR, as below with a single repeat of ***any*** of these parameters permitted to assess eligibility, if needed, at ***each*** of these 2 visits:

    - ALT <ULN *or* >5x ULN;
    - AST >5x ULN;
    - Alkaline phosphatase (ALP) >2x ULN;
    - Total bilirubin >ULN and direct bilirubin >ULN;
        - **Note:** Participants with a history of Gilbert syndrome would be eligible for this study provided direct bilirubin level is ≤ ULN, and hemoglobin and reticulocyte count are within the reference range of the Sponsor-identified central laboratory;
        - **Note:** If there is a >50% variability between the PreQ (***or*** PreQ repeat, if performed) and SCR results for ALT, AST, ***or*** alkaline phosphatase ***or*** total bilirubin is > ULN, these LFTs must be repeated 1 additional time, ≥2 weeks after SCR, with the variability between the PreQ (***or*** PreQ repeat, if performed) and the 1 additional measurement confirmed to be ≤50% for ALT, AST, ***and*** alkaline phosphatase, ***and*** total bilirubin ≤ ULN, **and** within the parameters above to confirm eligibility, as reported by the Sponsor-identified central laboratory, ***prior to*** progressing to the Run-In/Visit 2;
    - HbA1C >9% (75 mmol/mol), as assessed using NGSP certified method and standardized to DCCT assay;
    - Fasting Plasma Glucose >270 mg/dL (15 mmol/L);

- Fasting serum triglycerides >400 mg/dL (4.5 mmol/L);
- Platelet count < LLN;
- INR ≥1.3;
- Albumin < LLN;
- eGFR (using CKD-EPI-Cystatin-C) of <30 ml/min/1.73 m^2;
- A positive urine drug test for illicit drugs (with this 1 assessment ***not*** permitted to be repeated at *each* visit to confirm eligibility).

15. At PreQ *or* SCR, supine 12-lead ECG demonstrating QTc interval >480 msec ***or*** QRS interval >120 msec;

    - If QTc interval exceeds 480 msec or QRS interval exceed 120 msec, the 12-lead ECG should be repeated ***twice*** (on the same *or* different day) and the *average of three* QTc/QRS intervals used to determine eligibility;

        - **Note:** if ***uncorrected*** QT interval is >480 msec, this interval must be rate-corrected using the Fridericia method, with the resulting QTcF used for decision making and reporting.

Other Exclusions:

16. Participants meeting criteria for contraindication to undergoing imaging assessments at PreQ *and* SCR.

    - Active placement of medical devices in/on thoracic cavity – such as pacemakers, defibrillators [as these interfere with use of ultrasound based imaging modalities, and MRI];
    - History/evidence of ***any*** of the following:
        - Contraindication to MRI such as ferric implant;
        - History of severe claustrophobia impacting ability to perform MRI during the study even despite mild sedation/treatment with an anxiolytic;
        - Inability to lie still within the *closed* environment of the MRI scanner *or* maintain a breath hold for the required period to acquire images *even despite* mild sedation/treatment with an anxiolytic.

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

5.3. Randomization Criteria

A computer-generated randomization code using the method of random permuted blocks will be utilized to randomize participants equally balanced across the study interventions on Day 1/Visit 4 ***prior*** to the first dose of the double-blind, double-dummy study intervention provided participants satisfy ***all*** the following criteria:

1. Eligibility criteria outlined in Section 5.1 and Section 5.2;

2. A negative urine drug test for illicit drugs for sample collected at Baseline/Visit 3, as reported by Sponsor-identified central laboratory (with repeat assessment ***not*** permitted for this visit);

3. Fasting (≥8 hours overnight, with water permitted) serum triglyceride result of ≤400 mg/dL (4.5 mmol/L), for sample collected at Baseline/Visit 3, as reported by Sponsor-identified central laboratory;

    - A single repeat assessment permitted using Sponsor-identified central laboratory, though results of this repeat, when done, must be available ahead of randomization;

4. Fasting (≥8 hours overnight, with water permitted) plasma glucose result of ≤270 mg/dL (15 mmol/L), for sample collected at Baseline/Visit 3, as reported by Sponsor-identified central laboratory;

    - A single repeat assessment permitted using Sponsor-identified central laboratory, though results of this repeat, when done, must be available ahead of randomization, refer to Appendix 10.10.

5. In females, a negative ***serum*** pregnancy test result for sample collected at Baseline/Visit 3, as reported by Sponsor-identified central laboratory;

    - ***Plus,*** in females of childbearing potential, ***urine*** pregnancy test on Day 1/Visit 4, as reported on-site using supplies offered by Sponsor-identified central laboratory, must be negative for pregnancy, refer to Section 8.2.6;

6. In those with hypertension, BP controlled via adjustment of concomitant medications for BP control during the Run-In period with seated BP on Day 1/Visit 4 of <160/100 mmHg;

7. Compliance of ≥90% and ≤110% with ***doses*** of single-blind placebo administered (based on tablet count) from Baseline/Visit 3 to 1 day before Day 1/Visit 4, inclusive, refer to Section 6.4;

8. Total score of <8 on the AUDIT questionnaire, as assessed on Day 1/Visit 4;

9. An evaluable MRI-PDFF, as assessed by Sponsor-identified central imaging vendor, collected between Baseline/Visit 3 ***and*** prior to dosing with study intervention on Day 1/Visit 4.

5.4. Lifestyle Considerations

After confirmation of eligibility at PreQ ***and*** SCR, at **Run-In/Visit 2**, participants will be instructed to maintain the guidelines described below for the duration of their participation in the study. These guidelines must be reiterated on Day 1/Visit 4.

5.4.1. Contraception

The investigator or his or her designee, in consultation with the participant of childbearing potential, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 10.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA – Table 1, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4.2. Meals and Dietary Restrictions

1. Participants must abstain from all food and drink (except water) for **≥8 hours** prior to ***any*** blood sample collections for clinical laboratory tests, pre-dose PK, and exploratory biomarker related collections:

   - **Note:** Water may be consumed as desired (ad libitum).

2. Participants must abstain from all food and drink (though water is permitted) for **≥4 hours** prior to conduct of ***any*** of the imaging assessments – ie, MRI-PDFF, FibroScan® and Acuson Sequoia®.

3. Blinded study intervention must be administered twice daily with:

   - Morning dose at approximately 08:00 AM (±2 hours), local time with breakfast/meal;

   - Second dose, at approximately ≥8 and ≤12 hours after the morning dose, with the evening meal.

4. At scheduled outpatient visits to the site, in the morning, from Baseline/Visit 3 through Week 6/Visit 7, participants must be instructed to arrive without having consumed the morning meal/breakfast and without taking the morning dose of the blinded study intervention *and* concomitant medications for management of glycemic control (Section 6.5.1), lipid control (Section 6.5.2), and blood pressure (Section 6.5.3):

    - At Baseline/Visit 3 through Week 6/Visit 7, inclusive, following completion of ***all*** pre-dose procedures, the morning meal will be consumed with above-mentioned medications ***at the site***;

    - The morning meal during site visits will be *either* provided by the site, *or* the participant provided a voucher [or similar] by the site to purchase the meal before arriving at the site for each visit.

5. Participants will be counseled on appropriate dietary and lifestyle guidelines:

    - Counseling on dietary guidelines should be individualized in accordance with local medical standards of care for these participants and appropriate for the concomitant medical condition(s) of each participant;

    - Participants will be asked to maintain these guidelines throughout the study (ie, up to the Follow-up/Visit 8).

5.4.3. Alcohol, Caffeine, and Tobacco

- Intake of alcohol is permitted in moderation, refer to exclusion criterion 1 in Section 5.2 for limits on amount of alcohol consumption;

- Consumption of caffeinated drinks and nicotine-containing products is permitted during participation in the study, ***except:***

    - There *may* be a need for brief interruption while at the site and/or imaging facility, depending on local policy;

    - Consumption is *prohibited* for ***at least 1 hour*** prior to any vital sign measurement.

5.4.4. Activity

Participants will **not** be permitted to engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics):

- Within **48 hours** *before* each blood sample collection for clinical laboratory tests for the duration of participation in the study;

- Physical activity at an individual participant's normal pace is permitted.

5.4.5. Outpatient Visits to Site

- For each participant, every outpatient visit to the site is envisioned to occur with the participant arriving at the site between approximately 6 AM and 10 AM local time with each visit lasting approximately 2 hours.

- ***At selected visits***, to permit collection of post dose blood samples for PK, participants may either extend their stay on-site after dosing or leave and return later ***the same day,*** refer to Section 8.5 for details.

5.4.6. Outpatient Visits to Imaging/Radiology Facility

- Quantitative ultrasound-based assessments via FibroScan® *and* Acuson Sequoia® will occur either at the site **or** the imaging facility, depending on where these devices are located;

    - The location of these devices must be kept consistent at individual sites throughout study execution ie, *either* both devices reside at the site ***or*** both devices reside at the imaging facility – for the duration of the study;

- For each participant, the assessment of MRI-PDFF and quantitative ultrasound (via FibroScan® and Acuson Sequoia®) must occur at the same time of day (±2 hours) relative to 1st time of assessment while in study, ***as much as practically possible,*** refer to Section 8.6 for additional details.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

In this study, participants who screen fail in Part 1 may be considered for Part 2. ***In addition***, in rare cases, participants may be re-screened if due to logistical/administrative constraints, the maximum period between PreQ and Day 1/Visit 4, of 10 weeks, is exceeded. In ***both*** of these cases,

- Individual circumstances must be reviewed with a member of the Sponsor's Clinical team ***before*** the given participant is re-consented;

- All PreQ and SCR procedures must be repeated under a new 8-digit SSID number;

- Participants must be deemed to meet ***all*** the eligibility criteria including double confirmation of Sponsor-defined presumed NASH status under the new 8-digit SSID number.

6. STUDY INTERVENTION

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

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

- Placebo matching DGAT2i;
- Placebo matching ACCi;
- DGAT2i;
- ACCi.

6.1. Study Intervention(s) Administered

The following tablet strengths will be provided centrally by the Sponsor for use as study interventions in this study:

- For DGAT2i – 25 mg, 50 mg and 150 mg PF-06865571 tablets and matching placebo;
- For ACCi – 10 mg and 20 mg PF-05221304 tablets and matching placebo.

The study interventions above, will be packaged together in blinded blister cards, according to the treatment groups as noted in Table 4, and will be dispensed by the IRT system in sufficient quantities to enable dosing during the intervals between visits outlined in the SoA - Table 1. One extra blister card will be dispensed at *each* dispensation visit to support the flexibility provided by the visit windows. Each blinded blister card supports oral dosing for 7 days and will be labeled according to individual country regulatory requirements.

In Part 1, across the 5 treatment groups, double-blind, double-dummy administration of study intervention will be maintained as outlined in Table 4. Each dose will consist of 3 tablets, ie, 2 large tablets (DGAT2i/matching placebo) *plus* 1 small tablet (ACCi/matching placebo).

Table 4. Double-Blind, Double-Dummy Regimen in Part 1 of C3711005

Regimen			# of DGAT2i Tablets (mg strength)				# of ACCi Tablets (mg strength)		
			placebo	25	50	150	placebo	10	20
A	Placebo, BID	AM	2	-	-	-	1	-	-
		PM	2	-	-	-	1	-	-
B	DGAT2i 25 mg BID + ACCi 10 mg BID	AM	1	1	-	-	-	1	-
		PM	1	1	-	-	-	1	-
C	DGAT2i 100 mg BID + ACCi 10 mg BID	AM	-	-	2		-	1	
		PM	-	-	2		-	1	
D	DGAT2i 300 mg QD + ACCi 20 mg QD	AM	-	-	-	2	-	-	1
		PM	2*	-	-	-	1*	-	-
E	DGAT2i 300 mg BID + ACCi 10 mg BID	AM	-	-	-	2	-	1	-
		PM	-	-	-	2	-	1	-

* To maintain double-blind, double-dummy design across all groups, this group will receive placebo as evening dose.

For Part 2, updated dosing details will be offered via Investigational Product (IP) Manual for the site and *separately* for the participants via Dosing Diary Instructions once the data from Part 1 are reviewed and doses for Part 2 are identified.

6.1.1. Administration

Participants will either self-administer on-site (during scheduled visits) *or* at home/outpatient with meals – twice daily. Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing. Each day, the participants will be instructed to consume orally, the 3 tablets with the morning meal and 3 tablets with the evening meal as outlined in Table 4.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

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

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

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or Sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home for outpatient dosing by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

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

Upon identification of a product complaint, notify the Sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

The investigational product will be dispensed using the IRT system at visits identified in the SoA – Table 1. A qualified staff member will dispense the study intervention via unique container numbers on the blister cards provided, in quantities appropriate for the visit schedule. A second staff member will verify the dispensing.

The participant should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return all blister cards, both used and unused to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

6.3.1.1. Part 1

Approximately 90 participants will be randomized in a balanced ratio to receive either double-blind, double-dummy placebo, or 1 of 4 doses of DGAT2i + ACCi (with 3 entailing BID dosing of DGAT2i + ACCi *and* 1 dose-level of QD dosing but with blind maintained via dosing of placebo as the 2nd dose each day). A computer-generated randomization code using the method of random permuted blocks will be utilized to assign participants to any 1 of the 5 dosing groups on Day 1/Visit 4.

Allocation of participants to treatment groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the unique 8-digit participant number. The site personnel will then be provided with a treatment assignment, randomization number, and DU or container number(s) from the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number(s) assigned. The confirmation report must be stored in the site's files.

The investigational product will be dispensed at the study visits summarized in the SoA - Table 1; returned study intervention ***should not*** be redispensed to the participants.

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

6.3.1.2. Optional Part 2

The allocation of treatment in Part 2, will be in accordance to options described in Section 4.3.2, after the review of data from Part 1.

6.3.2. Breaking the Blind

The blind should ***only*** be broken in emergency situations for reasons of participant safety ***and*** when knowing the specific investigational product that the participant received alters the course of medical management.

The IRT will be programmed with blind breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

6.4. Study Intervention Compliance

Compliance with investigational product will be assessed at each on-site visit starting on Day 1/Visit 4 and continuing until Week 6/Visit 7, refer to SoA - Table 1. Compliance (as assessed by counting returned blister cards and/or tablets) will be defined as self-administration, by the participants, of:

- Baseline period (Visit 3 to 1 day prior to Day 1/Visit 4, inclusive): ≥90% and ≤110% compliance with single-blind, double-dummy, placebo based on the number of ***doses consumed*** for the ***specific*** duration of dosing; for example;
  - ***If*** duration of dosing was 12 days, participant can miss a maximum of **2 doses** (or take a maximum of 2 extra doses) ***and*** still qualify for randomization;
  - ***If*** duration of dosing was 16 days, participant can miss a maximum of **3 doses** (or take a maximum of 3 extra doses) ***and*** still qualify for randomization;
- Day 1/Visit 4 to last day of dosing *or* Week 6/Visit 7, inclusive: ≥80% compliance with self-administration of the study intervention is expected;
  - Investigators must closely monitor non-compliant participants in order to enhance participants' adherence to the study intervention;
    - *Post randomization*, at ***each*** dispensation visit (refer to SoA - Table 1), participants who are <80% compliant, based on tablet count *plus* review of dosing diary performed, must be re-educated by the site staff on the importance of daily self-administration of study intervention;
      - *Overall aim*: maintain ≥80% compliance over the duration of dosing with double-blind, double-dummy study intervention.

6.5. Concomitant Therapy

Given the relatively short duration of the double-blind, double-dummy dosing in this study, ***whenever possible***, attempts must be made to ***not*** alter the doses and regimens of the background/concomitant medications after randomization, Day 1/Visit 4 and until the required on-site Follow-up (ie, Visit 8).

All concomitant medications taken during the study must be recorded with indication of use. In addition, agents used for glycemic control, lipid control, and blood pressure control, daily dose, start and stop dates of administration must be captured. All participants must be questioned about concomitant medication at each outpatient visit to the site.

Medications started before **Day 1/Visit 4** will be documented as prior medications. Medications started after dosing of double-blind, double-dummy investigational product on Day 1/Visit 4 ***and*** until the required on-site Follow-up (ie, Visit 8), inclusive, will be documented as concomitant medications.

6.5.1. Medication for Glycemic Control

The use of the following classes of agents is **not** permitted within **8 weeks prior to SCR** visit and until the required on-site Follow-up (ie, Visit 8), inclusive:

- TZDs such as pioglitazone and rosiglitazone;
- Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, pramlintide).

Participants are permitted to be on stable doses of up to a ***maximum of 3 oral agents for glycemic control,*** starting at ≥**12 weeks prior to SCR** and until the required on-site Follow-up (ie, Visit 8), inclusive, across the country-specific, approved classes of agents including (but not limited to) the following:

- Biguanide such as metformin, refer to Appendix 10.9 for protocol-required dose-adjustment in participants on metformin dose >1 gm/day;
- Sulphonylureas such as acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, glyburide;
- Meglitinide analogues such as repaglinide, nateglinide;
- Dipeptidyl peptidase-IV inhibitors (DPP-IVi) such as sitagliptin, saxagliptin, vildagliptin;
- α-glucosidase inhibitors such as acarbose, miglitol;
- Sodium-glucose cotransporter 2 inhibitors such as canagliflozin, dapagliflozin, empagliflozin.

6.5.2. Lipid-modifying Medications

The use of any injectable agent (eg, those which inhibit monoclonal antibodies inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9) such as alirocumab, evolocumab, or inclisiran) is ***not*** permitted **within 12 weeks prior to SCR** and until the required on-site Follow-up (ie, Visit 8), inclusive.

Participants are permitted up to a ***maximum of 3 lipid-modifying oral agents*** if they are on stable doses, starting from ≥**12 weeks prior to SCR** and until the required on-site Follow-up (ie, Visit 8), inclusive, across the country-specific, approved classes of agents including (but not limited to) the following:

- Those on selected statins which are BCRP substrates will ***only*** be permitted *if on*:
  - Rosuvastatin doses up to 10 mg/day;
  - Atorvastatin doses up to 40 mg/day;
  - Simvastatin or Fluvastatin doses up to half-maximum in-country approved dose;

  Note: pravastatin and pitavastatin are permitted at doses up to the maximum approved, in-country dose;
- Bile acid sequestrants such as cholestyramine, colestipol, or colesevalam;
- Fenofibrate, a fibric acid derivative;
- Nicotinic acid/niacin;
- Ezetimibe.

Note: Use of gemfibrozil, an OATP inhibitor, is **not** permitted starting at Run-In/Visit 2 and until the required on-site Follow-up (ie, Visit 8) – participants on this agent, *at SCR*, will need to agree to be switched to another acceptable agent **starting at Run-In/Visit 2**, with stable dose of the acceptable agent achieved for ≥**4 weeks** before Day 1/Visit 4, in order to continue to randomization in this study.

6.5.3. Medications for Controlling Blood Pressure

Across the many classes of agents for management of hypertension, participants are permitted to be on stable doses of up to a ***maximum of 3 agents,*** starting at ≥**12 weeks prior to SCR** visit and until the required on-site Follow-up (ie, Visit 8), across the many approved classes of agents.

Note: **Starting at Run-In/Visit 2**, medications ± doses of medications for BP control can be adjusted to a maximum of 3 agents in order to meet BP criteria needed to progress to randomization [refer to Section 5.3].

6.5.4. Other Acceptable Concomitant Medications

As much as possible, participants on the following list of medications ***must be*** on stable doses (ie, **≥12 weeks prior to SCR** and until the required on-site Follow-up/Visit 8), inclusive]:

- Use of multi-vitamins is permitted though those on **Vitamin E** must be on stable dose for ***≥24 weeks*** before SCR;
- Use of aspirin at doses of ≤325 mg/day;

- Use of oral agents that alter stomach pH – eg, antacids, histamine-2 receptor antagonists, proton-pump inhibitors;

- Use of inhaled and topical corticosteroids;

  Note: Intercurrent treatment with systemic steroids, during participation in the study, may be permitted if treatment does/will ***not exceed 7 days***;

- Thyroid replacement therapy;

- Postmenopausal hormone therapy;

- Hormonal contraceptives that meet requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 10.4);

- Antipsychotic medications such as olanzapine, risperidone;

- Antidepressant medications such as tricyclic agents, selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors;

- Selected (herbal) supplements (***or*** approved agents), below, in countries where they are part of standard of care to lower LFTs (*based on limited/weak scientific evidence*);

  - Glutathione;

  - Glycyrrhizic acid;

  - Polyene phosphatidylcholine;

  - Silymarin;

  - Ursodeoxycholic acid;

- Chronic and intermittent use of NSAIDs (such as ibuprofen, ketoprofen, diclofenac, naproxen, indomethacin, meloxicam; and celecoxib) is permitted;

- Intermittent use of acetaminophen/paracetamol at doses up to 2 grams per day (for example: for short-term pain management) is deemed acceptable.

6.5.5. Prohibited Medications

- Certain medications for glycemic control, lipid-modification, and BP control are *not* permitted as per restrictions in Section 6.5.1, Section 6.5.2, or Section 6.5.3.

- Use of drugs historically associated with fatty liver are prohibited within **any ≥4 weeks interval** in the previous 12-months prior to SCR and until the required on-site Follow-up (ie, Visit 8), inclusive;

- *Examples* include amiodarone, methotrexate, *systemic* glucocorticoids (such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone), anabolic steroids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, valproic acid, other known hepatotoxins.

- Use of the following medications **within 12 weeks prior to** SCR and until the required on-site Follow-up (ie, Visit 8), inclusive, **is prohibited:**
  - *Chronic use* of immunosuppressants such as cyclosporine and tacrolimus;
  - Pharmacological agents with *approved indication* for weight loss such as orlistat and sibutramine;
  - Over-the-counter appetite- simulant or appetite- suppressant, as advertised;
  - P-gp substrates with narrow TI (eg, digoxin);
  - Potent inducers and inhibitors of CYP3A (refer to Appendix 10.8) including but not limited to the following:
    - Inducers – eg, rifampin, phenytoin, carbamazepine, St John's wort, phenobarbital;
    - Inhibitors – eg, ketoconazole/itraconazole, clarithromycin, many protease inhibitors;
  - CYP2C9 substrates with narrow TI (eg, warfarin or phenytoin);
  - Blood thinner(s) – eg, apixaban, dabigatran, rivaroxaban, edoxaban, fondaparinux, heparin, as well as Vitamin K antagonists (eg, warfarin);
  - Clinically significant OATP inhibitors – eg, cyclosporine, gemfibrozil, rifampin.

6.5.6. Rescue Medicine

There is no rescue therapy to reverse the AEs (including identified adverse drug reactions) observed with any of the study interventions; standard medical supportive care must be provided to manage the AEs.

Participant with T2DM with ***repeated*** fasting plasma glucose values >270 mg/dL (15 mmol/L) as reported by the Sponsor-identified central laboratory, at 2 sequential visits (eg, a combination of 2 consecutive scheduled visits ***or*** 1 scheduled visit followed by an unplanned visit to confirm the elevated result), post randomization, must ***either***:

- Have the dose of background metformin for glycemic control optimized, refer to Section 6.5.1 and Appendix 10.9;

- ***Or*** be withdrawn from the study (if ***not*** on metformin prior to randomization) for loss of glycemic control.

For the identified adverse drug reactions, guidance to investigators is offered (refer to Appendix 10.10 and Appendix 10.11) on the basis that reversal of effect towards baseline expected/observed in previous studies with ACCi upon discontinuation of study intervention.

6.6. Dose Modification

Dose modification of double-blind, double-dummy study intervention in individual participants in this study is not permitted to be modified.

The decision to pause *or* stop dosing at a study-level, for 1 or more active dose(s) of DGAT2i + ACCi may be considered based on recommendation from the IRC based on their review of unblinded, study-level emerging, *observed* safety data, refer to Section 9.6.

6.7. Intervention After the End of the Study

This is the first study to evaluate a range of doses of DGAT2i + ACCi. As such, multiple active groups are being included, to enable identification of efficacious dose(s) upon its' completion (not at start of study). In addition, considering duration of treatment period (ie, 6 weeks), benefit of the doses being studied cannot be claimed simply on the results from this study. Hence, study intervention will ***not*** be provided to participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See SoA - Table 1 and SoA - Table 2 for data to be collected at the time of discontinuation of study intervention.

7.2. Participant Discontinuation/Withdrawal from the Study

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

- Refused further follow-up;
- Lost to follow-up;
- Death;

- Study terminated by Sponsor;
- Discretion of the Investigator or Sponsor for safety or behavioral reasons, or the inability of the participant to comply with the protocol-required schedule of study visits or procedures at a given study site.

As soon as practically possible ***after*** the decision to withdraw from the study, an on-site visit should be considered:

- Participants should be questioned regarding their reason for withdrawal;
- See SoA – Table 1 and SoA - Table 2 – for assessments to be collected at the time of study discontinuation and follow-up for any further evaluations that need to be completed.

In this study, any participant who discontinues participation ***after the PreQ visit but prior to randomization and administration of the 1st dose of double-blind, double-dummy study intervention*** will have no additional procedures completed.

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures at PreQ. ***In addition***, a separate signed/dated ICD must be obtained before performing any study-specific procedures at SCR.

Study procedures and their timing are summarized in the SoA – Table 1 and SoA- Table 2. Protocol waivers or exemptions are not allowed. Safety issues should be discussed with the Sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention. Adherence to the study design

requirements, including those specified in the SoA – Table 1 and SoA - Table 2 - is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

The total blood sampling volume for individual participants in ***Part 1 of this study*** will be approximately 325 mL. Blood volume collected in Part 2 is envisioned to be the same as in Part 1 given intent to maintain the same design – refer to Section 4.1.2.

Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

No efficacy assessments are being undertaken in this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA – Table 1 and SoA - Table 2. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examinations

In this study, physical examinations are to be performed at nominal time points specified in the SoA – Table 1.

- A ***complete*** physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- A ***brief*** physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.1.1. Measurement of Waist Circumference

Waist circumference will be measured at the nominal time points specified in SoA - Table 1 using a flexible anthropometric tape and ideally, reporting the measurement in centimeters with accuracy to the nearest 0.1 centimeter (*or* 1/16th inch).

Measurement will be undertaken as follows:

- While participant is in a standing position with arms resting comfortably at the side;
- At the end of a normal expiration (when lungs are at their residual capacity);
- And the measurement will consider the following anatomical features as benchmarks:
  - Circumference of the narrowest part of the torso as viewed from the anterior aspect **or;**
  - If the narrowest part of the torso cannot be identified, the measurement must be made of the smallest horizontal circumference in the area between the ribs and the iliac crest.

8.2.2. Body Weight

In this study, assessment of body weight will occur at the nominal time points specified in SoA - Table 1 per the following specifications:

- Weight will be recorded using a scale placed on a stable, flat surface in a (semi)-private area;
- Same scale, as much as practically possible, will be used with the scale reporting weight in kilograms or pounds, and ***accuracy to the nearest 0.1 kg [or 0.2 pounds]*** -ie, the device used for this study must be able to distinguish a difference between 68.4 kg and 68.3 kg;
  - Measurement must be undertaken ***and*** documented to 1 decimal place;
- Assessment performed at approximately the same time of the day at each nominal time point, ***as much as practically possible***;
- Under standard conditions (eg, participants must wear light clothing with content of their pockets emptied or hospital gown and not be wearing shoes or bulky layers of clothing/jackets).

8.2.3. Electrocardiograms

Standard single 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in SoA – Table 1 using an ECG machine that automatically calculates the RR interval (or heart rate) ***and*** measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is ***not*** recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement.

- All scheduled 12-lead ECGs should be performed after the participant has rested quietly for ≥***10 minutes*** in a supine position;
- Starting at Day 1/Visit 4, if a machine-read QTc value is prolonged, as defined in Appendix 10.7, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range;
    - Assessment of whether prolonged QTc interval meets criteria as defined in Appendix 10.7, must assess QTc interval using ***only*** the Fridericia's correction (ie, QTcF) ***either*** as reported by the 12-lead ECG machine *or* QTcF derived using Sponsor-provided tool and reported QT and RR intervals;
    - In some cases, it may be appropriate to repeat abnormal 12-lead ECGs to rule out improper lead placement as contributing to the ECG abnormality; ***as much as practically, possible,*** it is important that leads be placed in the same positions each time in order to achieve precise ECG recordings.

Additional ECG values of potential clinical concern are listed in Appendix 10.7.

8.2.4. Vital Signs

In this study, assessment of vital signs (including seated blood pressure, and pulse rate) will occur at the nominal time points specified in SoA – Table 1 per the following specifications:

- At the PreQ visit, the participants' arm circumference should be measured (using a flexible anthropometric tape) at the midpoint of the length of the upper arm and the appropriate cuff selected and used throughout the study to measure BP/pulse rate via an automated device using an oscillometric method (not auscultation);
    - Participants with arm circumference greater than the largest cuff size available at each site are not eligible;
- ***Single seated*** blood pressure/pulse rate will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg, following a rest of ≥***5 minutes.***
- Same arm (preferably the dominant arm) will be used for blood pressure/pulse rate assessment throughout the study.

8.2.5. Clinical Safety Laboratory Assessments

See Appendix 10.2 for the list of clinical safety laboratory tests to be performed and SoA - Table 2 for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 10.2, must be conducted in accordance with the laboratory manual and SoA - Table 2. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within ***28 days after the last dose of study intervention*** should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

See Appendix 10.6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of ***at least 25 mIU/mL*** and performed using supplies offered by the Sponsor-identified central laboratory. Serum (all females) and urine pregnancy tests (in WOCBP) will be performed at the times listed in SoA - Table 2. Following a negative pregnancy test result at screening, appropriate contraception must be commenced (or continued) and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention (ie, single-blind, double-dummy placebo starting at Baseline/Visit 3 ***and*** double-blind, double-dummy study intervention starting at Day 1/Visit 4). Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be discontinued if the serum pregnancy result is positive.

8.2.7. Alcohol Intake Assessment

In this study, the ***interview-based*** AUDIT questionnaire[11] will be completed by the site staff based on responses offered by the participants – at the visits outlined in SoA – Table 1. Training for the site staff completing this questionnaire will be offered by the Sponsor as part of the protocol-specific training ahead of the initiation of the study.

8.2.8. Triggered Requirements and Individual Participant Stopping Rules

8.2.8.1. Potential Cases of Hypertriglyceridemia

In the current study, fasting serum triglycerides as reported by the Sponsor-identified central laboratory, with or without any accompanying signs/symptoms, will be assessed versus the threshold outlined in Appendix 10.10.

Individual participants with consistently increasing ***fasting*** serum triglycerides *over time* (***or*** double-confirmed result) ultimately reaching the threshold of ≥800 mg/dL (≥9 mmol/L) as outlined in Appendix 10.10 should stop dosing with study intervention and an AE of hypertriglyceridemia captured.

NOTE: dose(s) of background agent(s) for lipid control (refer to Section 6.5.2) must ***not*** be adjusted while in this study as it compromises ability to evaluate effectiveness of DGAT2i + ACCi to mitigate ACCi-induced elevations in serum triglycerides.

8.2.8.2. Potential Cases of Thrombocytopenia

In the current study, platelet count as reported by the Sponsor-identified central laboratory, with or without any accompanying signs/symptoms, will be assessed versus the threshold outlined in Appendix 10.11.

- In participants ***observed*** to have platelet count below the LLN should have an unplanned visit occur ***as soon as practically possible*** to:
  - Inquire about adverse events via open-ended inquiry;
  - *And* collect blood sample to permit safety-related laboratory assessments included hematology panel assessment by the Sponsor-identified central laboratory.

Participants observed to have a consistent decline *over time* (***or*** double-confirmed result) ultimately reaching the threshold of <75,000/mm^3 in platelet count as outlined in Appendix 10.11 should stop dosing with study intervention and an AE of thrombocytopenia captured.

8.3. Adverse Events and Serious Adverse Events

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention – (see Section 7.1).

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

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

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

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

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

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

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

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

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3 are recorded on the CRF. AEs and SAEs that begin after obtaining informed consent but before the start of study intervention will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. AEs and SAEs that begin after the start of study intervention are recorded on the AE section of the CRF.

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until ***at least 28 days*** after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

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

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Adverse Events of Special Interest

In this study, adverse event of special interest are the identified adverse reactions with administration of ACCi:

- Increase in *fasting* serum triglyceride result of ≥800 mg/dL (9 mmol/L) – refer to Appendix 10.10 ideally via double-confirmation provided participant is asymptomatic;

- Reduction in platelet count to <75,000/mm^3 – refer to Appendix 10.11 ideally via double-confirmation provided participant is asymptomatic.

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.3.1 through Section 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.7. Medication Errors

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

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

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

Medication errors include:

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

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

In the event of a medication dosing error, the Sponsor should be notified 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 nonserious, are recorded on the AE page of the CRF.

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

8.4. Treatment of Overdose

For this study, any dose of DGAT2i greater than 1800 mg, *or* any dose of ACCi greater than 200 mg, within a 24 hour time period will be considered an overdose.

Sponsor does ***not*** recommend specific treatment for an overdose. However, in the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until the study intervention can no longer be detected systemically (at least 5 days).

3. Obtain a blood sample for PK analysis as soon as practically possible.

4. Document the quantity of the excess doses as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with an SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

In this study, blood samples (**4 mL** each) to provide sufficient plasma for pharmacokinetic analysis of PF-06865571 and PF-05221304 will be collected into separate, appropriately labeled tubes containing K2-EDTA, at times defined in the SoA - Table 2. The date and time of 2 *most recent* ***doses*** should be noted in a dosing diary (or similar) by the participants prior to each scheduled, on-site visit; *plus date/time of double-blind, double-dummy study intervention taken on-site,* must be captured in the eCRF.

- The PK samples must be processed and shipped as indicated in the study-specific laboratory manual provided to the site, prior to initiation of study, to maintain sample integrity:
    - Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.
- *Any* of the following errors in *scheduled* collection of blood samples for PK (refer to SoA - Table 2) will be captured as protocol deviations even if results are deemed to be evaluable:
    - Predose collection (ie, C_{trough}) obtained post dose;
    - Post dose PK sample *not* collected within collection window following morning dose;
    - PK sample (pre- or post- dose) *not* collected.

- As part of understanding the pharmacokinetics of the study intervention, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes including endogenous biomarkers for drug metabolizing enzymes and/or drug transporters. These data will not be included in the clinical report.

- Samples will be analyzed for DGAT2i and ACCi using a validated analytical method in compliance with Pfizer standard operating procedures.

8.6. Pharmacodynamics

This study will assess effectiveness of DGAT2i + ACCi for reducing hepatic steatosis as assessed via MRI-PDFF. This evaluation however is labeled as a pharmacodynamic assessment (and ***not*** efficacy) in line with the evaluation being that of pharmacological activity.

8.6.1. Assessment of Liver Fat Using MRI-PDFF

At scheduled visits (refer to the SoA - Table 1), liver fat (via MRI-PDFF) and total liver volume (via MR volume acquisition protocol) will be assessed.

Transportation of the participants to the Imaging facility does ***not*** need to be supervised by the site staff. Each assessment will require the participants to be in a supine position in the confined space of the MRI scanner for approximately 25 minutes with the image acquisition undertaken **following a fast (except water) of ≥4 hours**, and ***as much as practically possible***, at the same time (±2 hours) of the day relative to assessment at Baseline (ie, between Baseline/Visit 3 and prior to 1st dose on Day 1/Visit 4).

Across the study sites, the Sponsor-identified central imaging vendor will train the staff at the imaging facility on the MRI acquisition protocols, 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**, 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 provided to the sites prior to the start of the study.

At the selected visits (refer to the SoA – Table 1) when liver fat is assessed via MRI-PDFF, additional MR sequences may be acquired for exploratory purposes including liver volume. These additional MR sequences and any additional MR endpoints, if analyzed, will *not* be included in the clinical study report but will be summarized via a standalone report.

Management of Incidental Findings

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

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

8.6.2. Assessment of Liver Fat and Stiffness – using FibroScan®

In this study, assessments of liver fat and stiffness using FibroScan® will occur at scheduled visits outlined in the SoA – Table 1. Each assessment will require the participants to be in a supine position for approximately 15 minutes with the image acquisition undertaken **following a fast (except water) of ≥4 hours**, and ***as much as practically possible***, at the same time (±2 hours) of the day relative to assessment at PreQ visit. The results for liver fat (via CAP™) in dB/m and liver stiffness (via VCTE™) in kPa to determine whether an individual participant qualifies at PreQ to progress to SCR will be displayed on the FibroScan® device at the end of each assessment. Acquisition results do not need independent over-reading, but steps to ensure that acquisition was complete and accurate are required. Training is to be offered to **at least 2 site staff** (who *may* be sonographers or comparable) by **EchoSens *and*** certified as operators based on this training by EchoSens, at the start of the study. *As much as practically possible*, attempts will be made to ensure each individual participants' assessment is performed by the same site staff throughout the study.

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

8.6.3. Assessment of Liver Fat and Stiffness – using Acuson Sequoia®

The assessment of liver fat (UDFF™ in %) and liver stiffness (via SWE™ in kPa) using Acuson Sequoia® will occur at scheduled visits outlined in the SoA – Table 1. Each assessment will require the participants to be in a supine position for approximately 15 minutes with the image acquisition undertaken **following a fast (except water) of ≥4 hours**, and ***as much as practically possible***, at the same time (±2 hours) of the day

relative to assessment at Baseline (ie, between Baseline/Visit 3 and prior to 1st dose on Day 1/Visit 4).

The results will be displayed on the Acuson Sequoia® device at the end of each assessment. Acquisition results do not need independent over-reading, but steps to ensure that acquisition was complete and accurate are required. Training is to be offered to **at least 2 site staff** (who *may* be sonographers or comparable) by **Siemens *and*** certified as operators based on this training by Siemens, at the start of the study. *As much as practically possible*, attempts will be made to ensure each individual participants' assessment is performed by the same site staff throughout the study.

The summary of numerical results (including quality-related outputs) must be printed and saved by the study site (or imaging facility, as applicable) as part of each participant's source documents. In addition, all images and output reports acquired must be saved by the study site until the conclusion of the study. The SWE endpoints, if analyzed, will not be included in the clinical study report but will be summarized via a standalone report.

Complete details regarding acquisitions using FibroScan® to assess CAP™ and VCTE™ as well as use of Acuson Sequoia® to assess liver fat (UDFF™ in %) and liver stiffness (via SWE™ in kPa) will be provided in a study-specific manual supplied by the Sponsor before initiation of this study.

Post-Hoc Analyses

As a means to understand the effects on liver fat, the Sponsor may undertake retrospective analyses of the participant-level, coded data acquired using 3 imaging modalities - ie, MRI-PDFF, FibroScan® and Acuson Sequoia®. Similarly, retrospective analyses of the participant-level, coded data may be undertaken to understand the performance of liver stiffness, as assessed using FibroScan® and Acuson Sequoia®. Any such analyses will ***not*** be included in the clinical study report; a separate supplemental report will be written to capture this work, if undertaken.

8.7. Genetics

8.7.1. Specified Genetics

A **4 mL** blood sample for DNA isolation, for pre-specified PGx, will be collected into plastic K2-EDTA tubes, as defined in SoA - Table 2. The DNA samples will be analyzed for the purpose of assessing the impact of allelic variants of SLCO1B1 (encodes for OATP1B1), SLCO1B3 (encodes for OATP1B3), SLCO2B1 (encodes for OATP2B1), SLC10A1 (encodes for NTCP), ABCG2 (encodes for BCRP), PNPLA3, and HSD17b13. As part of these analyses, genome-wide markers may be used to control for ethnic-based genetic associations. Additionally, these samples may also be used for retrospective evaluation of additional genetic variants associated with variation in PK, biomarker response, or to explore AEs should these be observed. Samples will be retained for a period of **up to 3 years after regulatory approval**.

See Appendix 10.5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in Sponsor-identified study-specific central laboratory manual.

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

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

Any data outside of the SLCO 1B1/1B3/2B1, SLC10A1, ABCG2, PNPLA3 and HSD17b13 genotyping will be used for internal exploratory purposes and will not be included in the clinical study report.

8.7.2. Banked Biospecimens for Genetics

A **4 mL** blood sample optimized for DNA isolation (Prep D1) will be collected as local regulations and IRBs/ECs allow – refer to SoA - Table 2.

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

See Appendix 10.5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in Sponsor-identified study-specific central laboratory manual.

8.8. Biomarkers

Blood, serum, *and* plasma samples for exploratory biomarkers (refer to Table 6) including NAFLD/NASH-related biomarkers, potential mechanism-related parameters, metabolic parameters, and aide in understanding the study interventions, will be collected at the nominal time points defined in the SoA - Table 2.

- Collection of these samples for exploratory biomarker research is part of this study;
- These samples must be processed and shipped as indicated in the study-specific laboratory manual provided by the Sponsor to the 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 as protocol deviation 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 scheduled collection prior to next dose of blinded study intervention, if undertaken postdose, 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 GLP standards, especially for these exploratory endpoints) but in all cases, the method will be in compliance with Pfizer standard operating procedures.

In addition, as part of further understanding the biological response to study intervention, samples may be used for evaluation of other related biomarkers as well as development and validation of bioanalytical methods. These data will be used for internal exploratory purposes and will ***not*** be included in the clinical study report.

8.8.1. Banked Biospecimens for Biomarkers

Additional Banked Biospecimens in this study are as follows and collected at the time points outlined in the SoA - Table 2:

- **4 mL** Prep B1.5 blood collection tube (for plasma);

- **6 mL** Prep B2.5 blood collection tube (for serum).

Banked Biospecimens will be collected as local regulations and IRB/ECs allow.

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

Collection of these samples for exploratory biomarker research is part of this study.

See Appendix 10.5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in Sponsor-identified study-specific central laboratory manual.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined in this section of the protocol 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. Estimands and Statistical Hypotheses

9.1.1. Estimands

Two estimands are defined for this study. **Estimand 1** will be used in Part 1 and Part 2 to support objectives related to imaging assessments for continuous endpoints assessed at Week 6. **Estimand 2** will be used in Part 1 and Part 2 to support all other objectives for continuous endpoints assessed over time.

Estimand 1: For a given endpoint, the estimand will be the estimated population based average treatment effect on natural log-transformed relative change from baseline for DGAT2i + ACCi relative to placebo ***at Week 6*** for all randomized/evaluable participants.

Intercurrent Events:

- Non evaluable baseline – All data collected post-randomization will be excluded.
- Withdrawal from study intervention after randomization – All data collected after a participant stops taking study intervention will be excluded.
- Prohibited medications – All assessments after a participant receives prohibited medications that would modulate the primary endpoint will be omitted from the analysis. The list of concomitant medications would be reviewed prior to database lock to determine which would be classed as "prohibited" for this estimand.
- Inadequate compliance – All randomized/evaluable participants with compliance <80%, over the ***entire duration of dosing*** with double-blind, double-dummy study intervention, will ***not*** have their endpoint measurement used as recorded in the analysis.

Population level summary:

- The population level summary will be the mean difference in natural log-transformed relative change from baseline between DGAT2i + ACCi groups and placebo groups for the endpoint of interest at Week 6.

Estimand 2: For a given endpoint, the estimand will be the estimated population based average treatment effect on natural log-transformed relative change from baseline for DGAT2i + ACCi relative to placebo ***over time*** for all randomized/evaluable participants.

Intercurrent Events:

- Non evaluable baseline – All data collected post-randomization will be excluded.
- Withdrawal from study intervention after randomization – All data collected after a participant stops taking study intervention will be included.
- Prohibited medications – All assessments after a participant receives prohibited medications that would modulate the endpoint will be omitted from the analysis. The list of concomitant medications would be reviewed prior to database lock to determine which would be classed as "prohibited" for this estimand.
- Inadequate compliance – All randomized/evaluable participants, *regardless of the level of compliance*, will have their endpoint measurement used as recorded in the analysis.

9.1.2. Hypothesis Tests

No formal hypothesis tests are planned for Part 1 or Part 2.

9.2. Sample Size Determination

9.2.1. Part 1

The proposed sample size for this study is approximately 90 participants randomized (18 participants per group) to ensure at least 75 participants (15 participants per group) offer evaluable data. With a sample size of 15 completers per group and with natural log-transformed SD of 0.221 for liver fat (assessed via MRI-PDFF), a 25% placebo-adjusted liver fat decrease can be detected at a significance level of 5% 1-sided with a power >90%.

9.2.2. Part 2

In Part 2, it is envisioned that number of participants randomized to each *active* dose of DGAT2i + ACCi or placebo *may* be adjusted. Those assigned to placebo *may* be reduced, given intent to pool data from all participants receiving placebo when summarizing end-of-study results. And while a maximum of 4 active doses (plus placebo) will be evaluated in Part 2, the total number of participants will not exceed 90 (with no more than approximately 27 participants per each *active* dose).

9.3. Analysis Sets

Data for any dose groups repeated in Part 1 and Part 2 (at a minimum placebo), will be pooled for purposes of summarizing end-of-study results and reporting these data in the clinical study report.

9.3.1. Part 1

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

Participants Analysis Set	Description
Enrolled	All participants who sign the preQ ICD.
Randomly assigned to investigational product	All participants randomly assigned to IP regardless of whether or not study intervention was administered.
Evaluable	All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the randomized intervention.
Safety	All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the product they actually received.
Defined Population for Analysis	**Description**
Estimand Set 1	All evaluable participants randomly assigned to study intervention and who take at least 1 dose of study intervention (ie Placebo/DGAT2i + ACCi).
PK Concentration Set	All participants randomly assigned to study intervention and who take at least 1 dose of DGAT2i + ACCi and in whom at least 1 concentration value is reported.

9.3.2. Part 2

Analysis set for Part 2 is envisioned to be identical to Part 1.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses of Part 1 (eg, interim analysis) are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints for Part 1 and optional Part 2 of the study.

9.4.1. Primary Endpoint(s)

Endpoint	Statistical Analysis Methods
Percent change from baseline in liver fat as assessed via MRI-PDFF at Week 6	• An ANCOVA analysis will be performed on the natural log-transformed relative change from baseline in fasting liver fat values at Weeks 6 from the Estimand Set 1 to estimate the treatment effect related to the Estimand 1. • The model will include treatment as fixed effect, baseline as a covariate effect. • No adjustments will be made for multiplicity.

9.4.2. Secondary Endpoint(s)

Endpoint	Statistical Analysis Methods
Percent change from baseline in fasting serum triglyceride levels over time	• A mixed model repeated measures (MMRM) analysis will be fitted to natural log-transformed relative change from baseline in fasting serum triglycerides at Weeks 2, 4, 6, and Follow-Up from the Estimand Set 2 to estimate the treatment effect related to the Estimand 2. • The MMRM will include treatment, time, and treatment-by-time interaction as fixed effects, baseline as a covariate effect and participant as a random effect. An unstructured correlation matrix will be used, and the Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. • Missing values will be imputed as part of the MMRM model assumptions. • No adjustments will be made for multiplicity.

9.4.3. Tertiary/Exploratory Endpoint(s)

Endpoints	Statistical Analysis Methods
Refer to Table 5	Will be described in the SAP finalized before any analyses of Part 1 (eg interim analysis).

Beyond the objectives, estimands, and endpoints outlined in Section 3 this study will also evaluate the objectives/endpoints summarized in Table 5.

Table 5. Additional Tertiary/Exploratory Objectives and Endpoints

Objectives	Endpoints
To evaluate concordance between effect on **liver fat** of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo, determined by MRI-PDFF, versus 2 different quantitative ultrasound techniques (CAP™ by FibroScan®, and UDFF™ by Acuson Sequoia®) in participants with presumed NASH	• Percent change from baseline at Week 6 in: • MRI-PDFF • CAP™ • UDFF™
To evaluate concordance between **liver stiffness** determined by 2 different quantitative ultrasound techniques (VCTE™ by FibroScan®, and SWE by Acuson Sequoia®) in participants with presumed NASH	• Values at baseline and Week 6 in: • VCTE™ • SWE™
To evaluate effect on **liver function tests** of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH	• Percent change from baseline, over time, in: • ALT • AST • Alkaline Phosphatase • Total Bilirubin and • GGT
To evaluate effect on **metabolic parameters** of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH	• Percent change from baseline, over time, in: • Total cholesterol • *Direct* LDL • HDL-C • *Direct* VLDL • Apolipoprotein A1, B_{total}, B_{100}, B_{48}, C3, and E • Change from baseline, overtime, in: • HbA1C • FPG • FPI • HOMA-IR
To evaluate the effect on mechanism/disease-related **biomarkers** of a range of DGAT2i doses coadministered with fixed dose of ACCi, compared to placebo in participants with presumed NASH	• Percent change over time in: • CK 18-M30, -M65 • Pro-C3, and Pro-C6 • PCSK9 • Adiponectin • hsCRP
To summarize plasma PK of DGAT2i and ACCi, across the active doses of DGAT2i + ACCi evaluated in participants with presumed NASH	Predose DGAT2i and ACCi plasma concentrations (ie, C_{trough})
To enable the exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision	Biobanking of blood-based specimens (including Prep D1, B1.5, and B2.5 collections to permit retrospective analysis of yet-to-be identified biomarkers) • These results may or may not be generated in the context of the present study

For ***all*** endpoints, baseline is defined as the evaluable result closest ***prior*** to dosing on Day 1.

9.4.4. Pharmacokinetic Analysis

All pharmacokinetic analyses will be performed on the PK concentration set.

Plasma concentration data for DGAT2i and ACCi will be listed and summarized (C_{trough} only) by treatment.

In addition, as permitted by data and determined by the Sponsor, exposure-response relationships between plasma concentrations of DGAT2i and/or ACCi and effect on primary, secondary and tertiary endpoints may be characterized using a population PK/PD approach. The objectives of such an analysis, if conducted, would aim to characterize exposure-response relationships and explore potential covariates (eg, age, race, gender, and body weight, etc.) influencing the observed PK and/or response to DGAT2i and/or ACCi. The population PK and/or PK/PD analyses, if conducted, will be reported separately from the main clinical study report.

9.4.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive study intervention (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations.

Endpoint	Statistical Analysis Methods
Secondary (refer to Section 3)	• The secondary endpoint will be analyzed in accordance with Pfizer Data Standards as above. • The primary analyses will be on the incidence and severity of all treatment emergent adverse events (TEAE), that will be reported by treatment group. The number of participants and percent will be presented.

The MedDRA dictionary will be used to classify all AEs with respect to system organ class and preferred term. Summaries of AEs will include treatment-emergent AEs according to treatment group.

9.4.5.1. Vital Signs Analyses

Changes from baseline in systolic blood pressure, diastolic blood pressure and pulse rate will be summarized by treatment and time. The number (%) of participants with maximum increases from baseline will be tabulated by treatment as defined in the SAP. Numbers and percentages of participants 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.

9.4.5.2. Electrocardiogram Analyses

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 participants with maximum increases from baseline will be tabulated by treatment as defined in the SAP. Numbers and percentages of participants 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.

9.4.6. Other Analyses

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

9.5. Interim Analyses

Interim analyses will be performed after completion of Part 1 (refer to Figure 1) to determine whether to conduct Part 2 and if so, guide selection of doses of DGAT2i and/or ACCi to evaluate in Part 2. Interim analysis results may be used to conduct a sample size re-estimation (eg, observed variability in Part 1 is higher than assumed for derivation of sample size for Part 1), facilitate PK/PD modeling, and internal business decisions regarding planning of future trials with DGAT2i and/or DGAT2i+ACCi. Before the interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Sponsor's SOPs will be documented and approved in an interim analysis SAP or final SAP.

9.5.1. PK/PD Modeling

A limited number of individuals not on the study team will be unblinded according to Sponsor SOPs with the purpose of composing PK/PD analysis sets and conducting PK/PD analysis. Data draws are expected at approximately 50%, and 100% of total study data from Part 1. These data are expected to include the primary endpoint (MRI-PDFF), plasma PK for DGAT2i and ACCi, fasting serum lipid parameters including fasted serum triglycerides (and fasted serum apolipoproteins, if available). Other data outlined in Table 5, may also be considered. The PK/PD analysis output at the completion of Part 1 (ie, achievement of LPLV in Part 1) will be shared as part of the planned Interim Analysis with selected members of the Sponsors' study team to enable decision to conduct Part 2 and if so, the dose(s) and dosing regimen(s) of DGAT2i + ACCi evaluated in Part 2.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC. The IRC will undertake periodic unblinded review of the safety data while the study is on-going. These reviews are envisioned, at a minimum, after approximately 33%, and 66%, of planned total sample size in Part 1 (and ***separately*** if conducted, Part 2), has been randomized. The IRC is independent of the study team and

includes 3 senior Sponsor colleagues members with no direct involvement in the conduct of the study. The IRC charter describes the role of the IRC in more detail.

- Across the IRC members, there will be at least 1 medically-qualified individual, and 1 statistician.

- The IRC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the IRC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

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

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

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

A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

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

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

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the Sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the Sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the Sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in ***the study monitoring plan***.

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

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

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

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

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

10.1.7. Source Documents

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

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

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

Definition of what constitutes source data can be found in the clinical monitoring plan.

Description of the use of computerized system is documented in the ***Data Management Plan***.

10.1.8. Study and Site Start and Closure

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

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

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the Sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

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

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

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

10.1.9. Publication Policy

The results from Part 1 and Part 2 are envisioned to be presented as a single pooled dataset at the end of the trial at a scientific meeting. Beyond this, the results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

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

10.2. Appendix 2: Clinical Laboratory Tests

Table 6 delineates the protocol mandated safety related laboratory tests and exploratory biomarkers to be collected following an overnight fast of ≥8 hours. The required blood and urine collections will be performed at times defined in SoA - Table 2. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

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

Table 6. All Planned Protocol Required Safety-Related Laboratory Tests and Exploratory Biomarkers in Study C3711005

Hematology	Chemistry	Urinalysis
– Hemoglobin – Hematocrit – RBC count – Reticulocyte count (Abs) – MCV – MCH – MCHC – Platelet count – WBC count – Total neutrophils (Abs) – Eosinophils (Abs) – Monocytes (Abs) – Basophils (Abs) – Lymphocytes (Abs)	–BUN –Creatinine –Cystatin-C (and eGFR using CKD-Epi-Cystatin-C) –*Plasma* Glucose (fasting) –Calcium –Sodium –Potassium –Chloride –Total CO_2 (bicarbonate) –AST (SGOT) –ALT (SGPT) –Total bilirubin –Alkaline phosphatase –GGT –Direct (conjugated) bilirubin –Indirect (unconjugated) bilirubin –Total bile acids –Creatine Kinase –Uric acid –Albumin –Total protein	–pH –Glucose (qual) –Protein (qual) –Blood (qual) –Ketones –Nitrites –Leukocyte esterase –Urobilinogen –Urine bilirubin –Microscopy[a]

Other

- HbA1C
- Coagulation (Plasma aPTT, PT, INR)
- Serum FSH[b]
- Serum and urine pregnancy test (refer to Section 8.2.6)
- Urine drug test[c]
- α1-antitrypsin[d]
- ceruloplasmin[d]
- Serology:[d] HBsAg, HCVAb (and if positive, reflex HCV RNA), HIV
- %CDT[e]
- Fasting serum Lipid Panel[f]

Additional exploratory biomarker assessments[g] include:	**Additional Tests for instances of suspected Hy's Law** [refer to Appendix 10.6]:
– Serum apolipoproteins A1, B_{total}, B_{100}, B_{48}, C3, E, and *direct* VLDL – Plasma Insulin – hs-CRP – CK18-M30, CK18-M65 – ProC3 and ProC6 – Plasma PCSK9 – Adiponectin – Pre-Specified PGx *and* Prep D1 (DNA) – Prep B1.5 (plasma) and B2.5 (serum) for mechanistic/disease-related biomarkers	– ALT, AST (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

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

b. Only in females, at PreQ, and SCR, *only.*

c. At PreQ, SCR, and Baseline/Visit 3, *only*; minimum requirement for urine drug test include cocaine, opiates/opioids, benzodiazepines and amphetamines.

d. At PreQ, and SCR, *only*.

e. At PreQ, SCR, Day 1/Visit 4, and Week 6/Visit 7.

f. Includes triglycerides, HDL-C, *direct* LDL-C, and total cholesterol.

g. At Baseline/Visit 3 and onwards, as per SoA - Table 2.

For list of terms corresponding to the abbreviations used herein, refer to Appendix 10.12.

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

10.3.1. Definition of AE

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

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

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

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

10.3.2. Definition of SAE

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

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

should be considered serious.

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE Recording/Reporting

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

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

Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and EDP supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- ***Mild***: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- ***Moderate***: An event that causes sufficient discomfort and interferes with normal everyday activities.

- ***Severe***: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the Sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal

relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is >100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies with DGAT2i and ACCi.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy;
    - Documented bilateral salpingectomy;

- Documented bilateral oophorectomy.

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

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

3. Postmenopausal female:

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

     - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

     - Female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.

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

    - Oral;
    - Injectable.

8. Sexual abstinence:

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

In addition, *one* of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

- Male *or* female condom with or without spermicide;
- Cervical cap, diaphragm, *or* sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

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

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to the study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

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

- The samples will be retained as indicated:

    - Samples for specified genetic analysis (see Section 8.7.1) will be stored for **up to 3 years** after regulatory approval or other period as per local requirements.

    - Samples for banking will be stored indefinitely or for another period as per local requirements.

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events

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

ECG Findings That <u>May</u> Qualify as Serious Adverse Events

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

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

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

ECG Findings That Qualify as Serious Adverse Events

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

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

10.8. Appendix 8: Strong CYP3A Inhibitors and Inducers

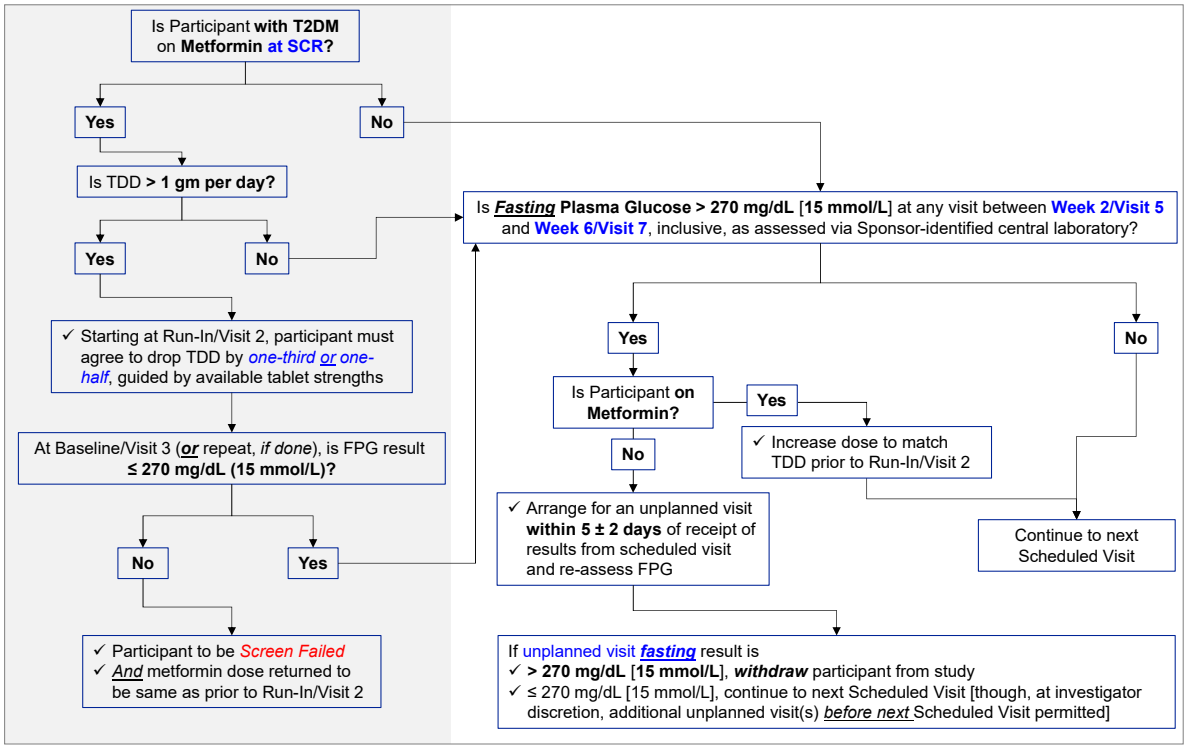
This list is not considered as exhaustive. Any questions regarding use of CYP3A inhibitors and inducers should be directed to the Sponsor study team.

CYP3A Inhibitors	CYP3A Inducers
HIV antivirals	**HIV antivirals**
Indinavir	Nevirapine
Nelfinavir	**Miscellaneous**
Ritonavir	Barbiturates
Saquinavir	Carbamazepine
Boceprevir	Glucocorticoids (systemic)
Lopinavir/ritonavir	Oxcarbazepine
Amprenavir	Phenobarbital
Atazanavir	Phenytoin
Telaprevir	Rifabutin
Darunavir/ritonavir	Rifampin
Fosamprenavir	St. John's wort[3]
Tiprinavir/ritonavir	Troglitazone
Antibiotics	Nafcillin
Clarithromycin	Avasimibe[4]
Troleandomycin	Enzalutamide
Telithromycin	Mitotane
Anti-infective	
Itraconazole	
Ketoconazole	
Posaconazole	
Voriconazole	
Miscellaneous	
Nefazodone	
Grapefruit juice[1]	
Conivaptan	
Mibefradil[2]	
Idelalisib	

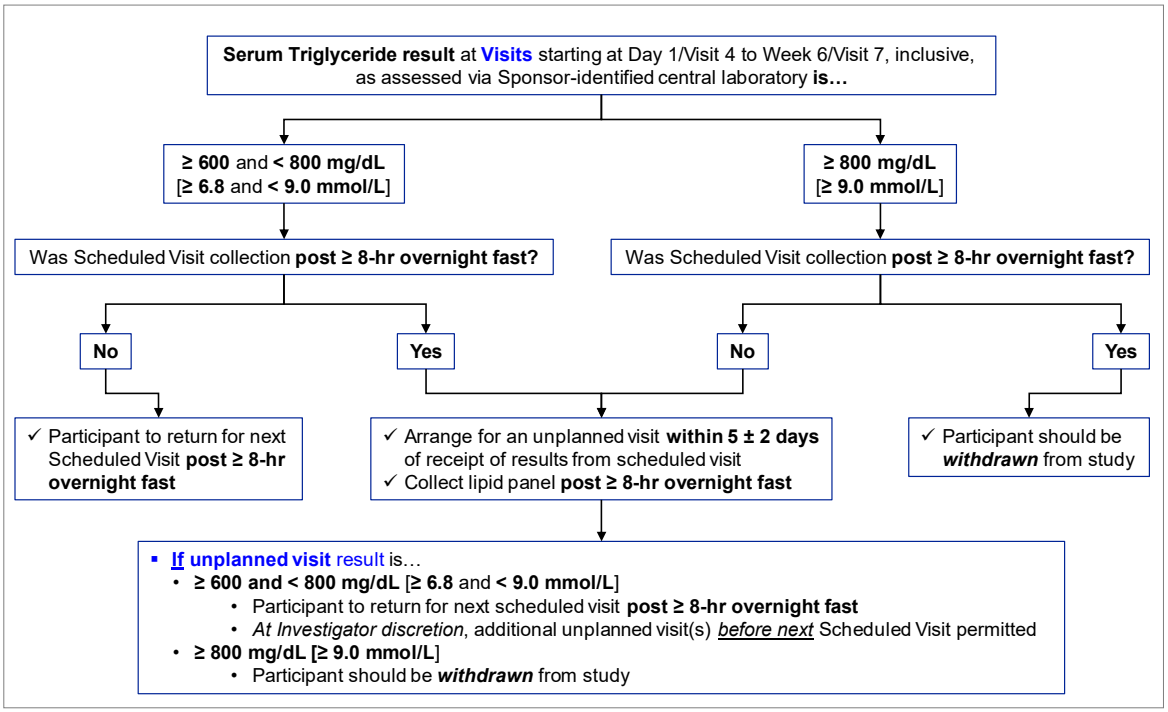
1. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when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

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.

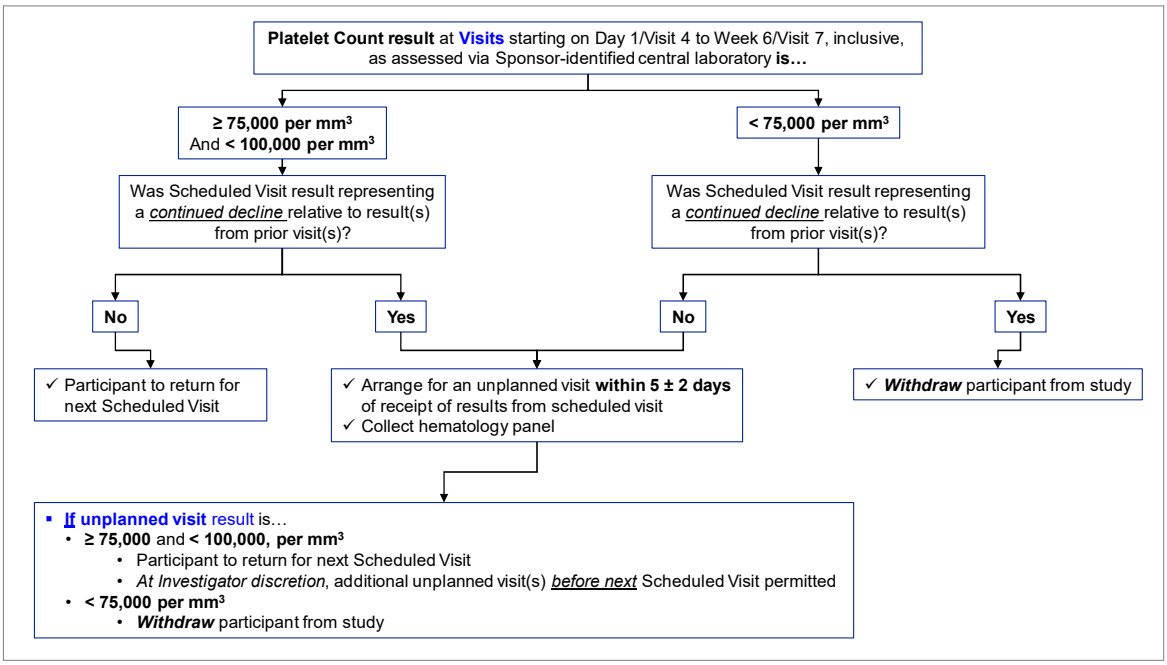
10.9. Appendix 9: Guidance to Investigators – Management of Individual Participants Glycemic Control – *including Metformin Dose Starting at Run-In/Visit 2*



10.10. Appendix 10: Guidance to Investigators – Management of Individual Participants with Elevation in Fasting Serum Triglycerides



10.11. Appendix 11: Guidance to Investigators – Management of Individual Participants With Decrease in Platelet Count



10.12. Appendix 12: Abbreviations

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

Abbreviation	Term
%CDT	percent carbohydrate deficient transferrin relative to total transferrin
A1AT	Alpha-1-antitrypsin
ABCG2	constitutively expressed ATP-binding cassette transporter
Abs	Absolute
ACC	acetyl-CoA carboxylase
ACCi	acetyl-CoA carboxylase inhibitor (PF-05221304)
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
Apo	Apolipoprotein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{tau}	area under the concentration-time curve from time 0 to end of dosing period
AUDIT	Alcohol use disorders identification test
AV	Atrioventricular
BBS	Biospecimen Banking System
BCRP	breast cancer resistant protein
BID	bis in die (twice-a-day)
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CAP™	Controlled attenuation parameter
CDT	Carbohydrate deficient transferrin
CFR	code of federal regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatinine kinase
CK18-M30	cytokeratin-18-M30 fragment
CK18-M65	cytokeratin-18-M65 fragment
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
C_{max}	peak or maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CoA	coenzyme A
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form

Abbreviation	Term
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
C_{trough}	plasma concentration before next dose
CYP	Cytochrome P-450 (3A, 2B6, 2C9, 2C19)
D/C	Discontinue
DAG	Diacylglycerol
dB/m	decibels per meter
DCCT	Diabetes Control and Complications Trial
DDI	drug drug interaction
DGAT1	diacylglycerol acyltransferase 1
DGAT2	diacylglycerol acyltransferase 2
DGAT2i	diacylglycerol acyltransferase 2 inhibitor (PF-06865571)
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DNL	de novo lipogenesis
DPP-IVi	dipeptidyl peptidase-IV
DU	dispensing Unit
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
ED_{50}	dose that produces half maximum drug effect
EDP	exposure during pregnancy
EFD	embryo-fetal developmental
eGFR	estimated glomerular filtration rate
EMA	European Medical Agency
EU	European Union
EudraCT	European Clinical Trials Database
F/U	follow-up
FFA	free fatty acid
FPG	fasting plasma glucose
FPI	fasting plasma insulin
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HbA1C	glycated hemoglobin
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV RNA	hepatitis C virus genetic material (ie, Ribonucleic acid)
HCVAb	hepatitis C virus antibody
HDL-C	high density lipoprotein cholesterol
HIPPA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance

Abbreviation	Term
HR	heart rate
HRT	hormone replacement therapy
hs-CRP	high-sensitive C-reactive protein
HSD17b13	17β-Hydroxysteroid dehydrogenase type 13
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IPAL	Integrated Path to Architectural Licensure
IRB	Institutional Review Board
IRC	internal review committee
IRT	interactive response technology
IWR	interactive web response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
kPa	kilopascals
LDL-C	low density lipoprotein-cholesterol
LFTs	liver function tests
LLN	lower limit of normal
LPLV	last participant last visit
LS	least square
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MELD-Na	model of end-stage liver disease including serum sodium (in addition to serum creatinine, bilirubin, and INR)
MMRM	mixed model repeated measure
MR	magnetic resonance
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging using proton density fat fraction acquisition
N/A	not applicable
NAFLD	nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NGSP	National Glycohemoglobin Standardization Program
NOAEL	no observed adverse effect level
non-HDL	non-high density lipoprotein cholesterol
NSAIDs	non-steroidal anti-inflammatory drugs
NTCP	sodium-dependent uptake transporter
NYHA	New York Heart Association
OAT	organic anion transporter (P1B1, P1B3, P2B1)
OATP	organic anion-transporting polypeptide

Abbreviation	Term
OCT2	organic cation transporter 2
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamics
PE	physical exam
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PI	principal investigator
PK	Pharmacokinetics
PK/PD	pharmacokinetic-pharmacodynamic
PNPLA3	patatin like phospholipase domain containing protein 3
PreQ	prequalification visit
ProC3	N-terminal propeptide of type III procollagen
ProC6	C-terminal fragment of α3 chain of procollagen type VI
PT	prothrombin time
PVC	premature ventricular contraction
Q12H	every 12 hours (eg, dosing)
Q8H	every 8 hours
QD	quaque die (once-a-day)
QRS	combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	QT interval corrected for heart rate
QTcF	Fridericia's formula, a correction formula for the QC interval
RBC	red blood cell
RNA	ribonucleic acid
RR	interval between 2 successive R waves in a QRS complex
SAE	serious adverse event
SAP	statistical analysis plan
SCR	Screen/Visit 1
SD	standard deviation
SGOT	serum glutamic oxalo-acetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLC10A1	solute carrier Family 10 Member 1
SLCO	solute carrier organic transporter family member (1B1, 1B3, 2B1)
SoA	Schedule of Activities
SOP	standard operating procedure
SREBPs	sterol regulatory-element binding proteins
SRSD	single reference safety document
SSID	service set identifier
SUSAR	suspected unexpected serious adverse reaction
SWE	Sheer wave elastography
$t_{1/2}$	terminal half-life
T1D	type 1 diabetes
T2DM	type 2 diabetes mellitus
TBili	total bilirubin
TEAE	treatment-emergent adverse event

Abbreviation	Term
TI	therapeutic index
TZD	Thiazolidinediones
UDFF™	ultrasound-derived fat fraction
ULN	upper limit of normal
US	United States
VCTE™	Vibration-Controlled Transient Elastography
VLDL	very low-density lipoprotein
WBC	white blood cell
WOCBP	women of childbearing potential

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