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CLINICAL STUDY PROTOCOL

An Investigator-Initiated Open-Label, Randomized Study of Gemcabene in Adults with Familial Partial Lipodystrophy Disease (FPLD)

Investigational Product: Gemcabene calcium tablets (gemcabene)
Protocol Number: HUM00130803/GEM-IIT-602

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Confidentiality Statement

SIGNATURE PAGE

STUDY TITLE: An Investigator-Initiated Open-Label, Randomized Study of Gemcabene in Adults with Familial Partial Lipodystrophy Disease (FPLD)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date

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SYNOPSIS

TITLE: An Investigator-Initiated Open-Label, Randomized Study of Gemcabene in Adults with Familial Partial Lipodystrophy Disease (FPLD)

PROTOCOL NUMBER: HUM00130803 / GEM-IIT-602

INVESTIGATIONAL PRODUCT: Gemcabene calcium tablets (gemcabene)

PHASE: Investigator Initiated IND Phase I/II

INDICATION(S): Treatment with gemcabene is indicated as an adjunct standard of care to diet to reduce triglyceride (TG) levels and indicators of nonalcoholic fatty liver disease (NAFLD) in adult patients with Familial Partial Lipodystrophy Disease (FPLD)

OBJECTIVE:

The overall objective of this study is to assess the efficacy and safety of two dosing regimens of gemcabene (300 mg once daily (QD) for 24 weeks or 300 mg QD for 12 weeks followed by 600 mg QD for 12 weeks) in up to eight patients with FPLD with elevated TGs and NAFLD.

POPULATION:

Up to eight male and female patients, ≥18 years of age with confirmed FPLD will be enrolled in the study. Patients must have a fasting TG value ≥250 mg/dL and quantifiable hepatic steatosis (as determined by magnetic resonance proton density fat fraction [MRI-PDFF] – Stage 2 or 3) while on a stable, low-fat, low-cholesterol diet (per self-report).

STUDY DESIGN:

Although this is a pilot INDstudy, measures must be put in place to stabilize TG measures at baseline and concomitant TG-lowering therapies to ensure the collection of meaningful data during study conduct.

Pre-Screening Visit/Wash-Out Period: A Pre-Screening Visit followed by a Wash-Out Period will be required for eligible patients taking fibrates, niacin ≥250 mg/day or over-the-counter fish oil or other products containing omega-3 fatty acids (OMG-3), or thiazolidinediones (TZDs). For patients requiring a Wash-Out Period, the Pre-Screening Visit will be their first study visit and will occur prior to the Screening Visit based on the duration of the Wash-Out Period required.

Patients currently taking fibrates, niacin ≥250 mg/day, prescription or over-the-counter fish oil or other products containing OMG-3, or TZDs must be able to safely discontinue therapy at screening. The Wash-Out Period will be six weeks. If patients are on metreleptin for investigational use, they should be washed out for four months and their leptin level must have returned to pre-metreleptin treatment state, which is indirect evidence that any binding antibodies may have decayed as well.

Screening Period: All eligible patients will participate in the Screening Visit up to 28 days prior to Day 1. For eligible patients taking stable, allowable, lipid-lowering therapy (statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, or other herbal products or dietary supplements with potential lipid-altering effects) for greater than six weeks and who do not require a Wash-Out Period, the Screening Visit will be their first study visit.

At the end of the two-to four-week diet and lifestyle stabilization and TG qualifying period, eligible patients must have a fasting TG ≥ 250 mg/dL prior to their MRI-PDFF performed at Visit S2. The TG level for qualification will be based on Visit S1. If a patient's TG value from Visit S1 falls outside the required range for entry into the study, one additional sample for fasting TG measurement can be collected between Visits S1 and S2.

At Visit S2 potential patients must have hepatic steatosis ≥10% based on the core imaging lab assessment of liver fat content (MRI-PDFF) to be eligible for enrollment on Day 1 (Visit T1). If the core imaging lab assessment of liver fat content is below the minimum range outlined in the protocol the patient will be ineligible and will not be eligible for re-screening. A determination of hepatic fibrosis (MR elastography) will also be performed at this visit.

Patients meeting screening criteria including TG and 10% liver fat will be offered an optional liver biopsy which will be performed for the assessment of a baseline NAFLD Activity Score (NAS). If patients opt-out of the liver biopsy, they can still move to the treatment phase.

Open-label, Randomized Treatment Period: After confirmation of qualifying fasting TG values and MRI-PDFF confirmed hepatic steatosis ≥10%, eligible patients will have a fasting, optional liver biopsy performed, if they opt in, and enter the treatment phase to receive 300 mg gemcabene daily for 12 weeks starting on Day 1/Visit T1. Up to eight patients will be treated. After 12 weeks at visit T4, patients will be randomized 1:1 according to a pre-generated randomization code to the remaining 12 -week treatment period to one of the following groups:

- Group 1: Gemcabene 300 mg QD for 12-24 weeks
- Group 2: Gemcabene 600 mg QD for 12-24 weeks

The primary evaluation of TG efficacy will be after 12 weeks of treatment. The primary evaluation for the secondary parameters of liver fat (MRI-PDFF) and NAS (histology) will be at 24 weeks. The Follow-up Visit will occur four weeks (±3 days) after the last dose of study drug.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

The tablet drug product for oral administration is an immediate-release tablet containing 300 mg of the parent gemcabene in a formulation comprising the following inactive ingredients: lactose monohydrate, hydroxypropyl cellulose, croscarmellose sodium magnesium stearate, Opadry® White YS 1-7040, and Simethicone.

Study drug will be packaged in high-density polyethylene bottles with child-resistant closures.

- 300 mg: one 300 mg tablet orally QD, or
- 600 mg; two 300 mg tablets orally QD.

Patients will be instructed to take study drug at the same time in the morning either with or without food.

PRIMARY AND SECONDARY EFFICACY ENDPOINTS:

Primary Efficacy Endpoint:

The primary endpoint of this study is the percent change from baseline to Week 12 in fasting serum TG.

Secondary Efficacy Endpoints:

The secondary endpoints are as follows:

- Change and percent change in fasting serum TG from baseline to average of Weeks 6 and 12, and Week 24 and change in fasting serum TG from baseline to Week 12;
- Change and percent change in liver fat content as determined by MRI-PDFF from baseline to Week 12 and Week 24;
- Change and percent change in hepatic fibrosis as determined by MR elastography from baseline to Week 12 and Week 24;
- Change and percent change in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) (ultracentrifugation), apolipoprotein B (apo B), ApoA-1, ApoA-II, ApoA-V from baseline to Weeks 12 and 24;
- Change and percent change in high-sensitivity C-reactive protein (hsCRP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) from baseline to Weeks 12 and 24.

Exploratory Endpoints:

Exploratory endpoints will be analyzed from previously collected data or reserve samples if the above analyses show benefit:

The exploratory efficacy endpoints are as follows:

- Change and percent change in additional biomarkers of hepatic steatosis including AST/ALT ratio; γ-glutamyl transpeptidase, (GGT); alkaline phosphatase; international normalized ratio (INR), albumin, total bilirubin from baseline to Week 12 and Week 24;
- Liver mRNA levels which may include denovo cholesterol synthesis and lipogenesis, inflammation, LDL receptor, β-oxidation, and sulfatase from baseline to Week 24;
- Change and percent change in leptin, adiponectin and fasting insulin levels, fasting plasma glucose (FPG), and hemoglobin A1c (HbA1c), non-high-density lipoprotein cholesterol (non-HDL C), very low density lipoprotein cholesterol (VLDL-C), ApoC-II, ApoC-III, ApoE, and Lp(a) from baseline to Week 12 and Week 24;
- Change and percent change in interleukin-6 (IL-6), interleukin 1β (IL-1β), angiopoietin like 4 transpeptidase (ANGPTL4), angiopoietin like 3 transpeptidase (ANGPTL3), fibrinogen, and serum amyloid A (SAA) from baseline to Weeks 12 and 24;

- Change and percent change in NAS (NAFLD activity score)[23] including steatosis, lobular inflammation and hepatocyte ballooning from baseline to Week 24;
- Change and percent change in quality of life (QOL) measures including visual analog scale (VAS) of pain and short form-36 (SF-36) from baseline to Weeks 12 and 24.

SAFETY VARIABLES:

The safety variables include adverse events, safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) with particular attention to hepatic (e.g., ALT/AST, bilirubin, alkaline phosphatase, GGT, renal (e.g., blood urea nitrogen [BUN], serum creatinine, protein:creatinine ratio, albumin/creatinine ratio, urinalysis sediments, pH, electrolytes), and skeletal muscle toxicities (i.e., creatine kinase), ketone bodies, 12-lead electrocardiograms (ECGs), physical examinations, and vital signs.

STATISTICAL METHODS:

Patient Populations:

The Full Analysis Set (FAS) is defined as all randomized patients who received at least one dose of study drug, and have both a baseline and at least one post-baseline lipid value. All efficacy summaries and analyses will be performed using the FAS.

The Safety Analysis Set (SAS) is defined as all randomized patients who received at least one dose of study drug. All safety summaries will be performed using the SAS.

Primary efficacy analyses:

The primary efficacy endpoint is the percent change from baseline to Week 12 in fasting serum TG. If the Week 12 TG value is missing, then the "Week 12" TG value will be imputed using last observation carried forward (LOCF).

Baseline will be defined as the average of the pre-dose Day 1/Visit T1 value and the last qualifying screening visit.

The primary efficacy endpoint will be summarized by treatment group and timepoint using the FAS.

Secondary efficacy analyses:

The secondary TG efficacy endpoints are the change from baseline to Week 12 and change and percent change from baseline to the average of Weeks 6 and 12, and Week 24 in fasting serum TG. Baseline will be defined as outlined above for the primary variable. For the "average of Weeks 6 and 12" TG efficacy assessment, if only the Week 6 or Week 12 TG value is available, then that single value will be used. If both the Week 6 and Week 12 TG values are missing, then the average "Week 6 and Week 12" TG value will be imputed using LOCF. For the "Week 24" TG efficacy assessment, if Week 24 values are missing, then the value will be imputed using LOCF.

The change and percent change in all other secondary efficacy biomarkers will be summarized for Week 12 and Week 24 as described above.

An additional secondary analysis is change and percent change from baseline to Week 12 and Week 24 in the percentage of liver fat content as measured by MRI-PDFF. Baseline liver fat content is defined as the value from Screening. Missing percentage liver fat content at Week 24 will be imputed using LOCF. It will be summarized by treatment group and timepoint using the FAS. Hepatic fibrosis as measured by MR elastography will be summarized as outlined above for liver fat content via MRI-PDFF.

An additional secondary analysis in change and percent change from baseline to Week 24 in NAS as determined by histology. It will be summarized by treatment group at Week 24 using the FAS.

Exploratory efficacy analyses:

The exploratory variables (if determined as necessary) will be summarized as described for the secondary endpoints above. Missing values will be imputed using LOCF.

Safety analyses:

Safety will be assessed using the SAS. The assessment of safety will include adverse events, clinical laboratory assessments, ECGs, physical examinations, and vital signs. The safety analysis will be based primarily on the frequency of new or worsening adverse events, laboratory abnormalities, and SAEs. Other safety data will be summarized as appropriate.

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group, system organ class, and preferred term.

Safety laboratory data will be summarized by treatment group at baseline (pre-dose Day 1/Visit 1 value), End of Treatment (Week 24), or the ET Visit, if applicable, and change from baseline to End of Treatment (Week 24) or the ET Visit, if applicable. Frequency counts of new or worsening abnormalities will also be provided.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance model
ANGPTL4	Angiopoietin like 4
Apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CI	Confidence interval
CK	Creatine kinase
CRA	Clinical research associate
CTA	Clinical trial authorization
CVD	Cardiovascular disease
CYP	Cytochrome P450
EC	Ethic Committee
ECG	Electrocardiogram
CRF	Case report form
EDC	Electronic data capture
ET	Early Termination
FAS	Full analysis set
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HIV	Human immunodeficiency virus
hsCRP	High-sensitivity C-reactive protein
IL-6	Interleukin 6
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IWRS/IVRS	Interactive web/voice response system

Abbreviation	Definition
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
LPL	Lipoprotein lipase
LSM	Least squares mean
MedDRA	Medical Dictionary for Regulatory Affairs
NCEP ATP-III	National Cholesterol Education Program Adult Treatment Panel III
NGAL	Neutrophil gelatinase-associated lipocalin
NIMP	Non-investigational medical product
non-HDL-C	Non-high-density lipoprotein cholesterol
OMG-3	Omega-3 fatty acids
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetics
PPS	Per protocol set
QD	Once daily
SAA	Serum amyloid A
SAE	Serious adverse event
SE	Standard error
SHTG	Standard Operating Procedure
SOP	Severe hypertriglyceridemia
TC	Total cholesterol
TG	Triglyceride
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background

Gemcabene calcium is the monocalcium salt of a dialkyl ether dicarboxylic acid having 2 terminal gem dimethyl carboxylate moieties. Gemcabene has a dual mechanism of action that involves: (1) enhancing the clearance of very-low density lipoprotein cholesterol (VLDL); and (2) blocking the overall production of hepatic triglyceride (TG) and cholesterol synthesis.

Gemcabene enhances the clearance of VLDL by decreasing the production of messenger RNA (mRNA) of the *APOC3*gene, thereby decreasing the production of the ApoC-III protein [1]. This in turn unmasks apolipoprotein E (ApoE) which (1) enhances the clearance of the VLDL remnants via ApoE remnant receptors; (2) reduces the formation of low-density lipoprotein (LDL) particles; and (3) enhances lipoprotein lipase mediated TG lipolysis allowing increased delivery of fatty acids to muscle and adipose tissue.

Gemcabene may also block the overall production of hepatic TG and cholesterol. Given its structural similarities to long-chain fatty acid, gemcabene may act as an inhibitor of acetyl CoA acetytransferase (ACC), subsequently leading to a decrease in hepatic TG production [2]. Gemcabene may also inhibit one or more enzymes in the cholesterol synthesis pathway leading to less cholesterol in the cell, thereby upregulating LDL receptors in the liver.

In inflammatory states, cytokines, such as interleukin-6 (IL-6) and interleukin 1-beta (IL1-b), activate nuclear hormone receptors (NHRs), such as C/EPB-b, C/EPB-d and nuclear factor kappa B (NF-kB), and lead them to bind to the C-reactive protein (CRP) promoter and increase CRP mRNA production. Based on preclinical studies, gemcabene may inhibit the interaction of these NHRs on the CRP promoter and therefore reduce CRP mRNA production [3].

Taken together, gemcabene's mechanism of action should lower the full range of atherogenic particles (VLDL, IDL, and LDL) resulting in decreases in atherogenic particle number (ApoB), particle cholesterol (non-HDL-C) and TG (when elevated); with concomitant lowering of hsCRP.

As such, the effects of gemcabene were explored in a pre-clinical model of NAFLD (STAM mice). Overall, gemcabene showed an anti-fibrotic effect, as well as demonstrating anti-NASH and hepatoprotective effects on the liver pathology in this model. Treatment with middle and high doses of Gemcabene reduced the mRNA expression levels of inflammation related genes (TNF-α, Monocyte chemotactic protein-1 (MCP-1), Macrophage inflammatory protein-1 (MIP-1β), CCR5, CCR2, NF-kβ), supporting hepatoprotective property. Gemcabene decreased plasma CRP levels, which was in agreement with human data [4]. The preclinical data is supportive of the potential for gemcabene to elicit beneficial effects in hepatic steatosis.

Gemcabene-calcium rapidly converts to gemcabene free acid when in contact with the gastric fluid. Gemcabene is rapidly absorbed following oral administration. It distributes to the liver where it has its effect as the active molecule, with exposure increasing approximately linearly with dose. Steady state concentrations are achieved within six days of repeated dose administration, with an average half-life from 32 to 41 hours. Gemcabene's primary route of metabolism and elimination is renal, predominantly as a gemcabene glucuronide formed in the kidney.

1.2 Rationale

Patients with typical Familial Partial Lipodystrophy Disease (FPLD) have a marked loss of subcutaneous fat from the extremities and trunk accompanied by a variable amount of excess fat deposition in the nonlipodystrophic areas such as the face, chin, back, and intraabdominal regions [5-7]. Dietary fat restriction and other lifestyle changes are first line therapy to avoid weight gain, critical for effective management of metabolic complications in patients with lipodystrophy. However, despite lifestyle changes and conventional hypoglycemic and hypolipidemic therapies, some FPLD patients continue to have extreme hypertriglyceridemia, hepatic steatosis, and poorly controlled diabetes [8,9].

Hypertriglyceridemia is a common condition of FPLD and serum triglyceride levels of 250–1999 mg/dL, classified as moderate to severe hypertriglyceridemia, indicate risk for development of very severe hypertriglyceridemia, causative of pancreatitis and hepatic steatosis [10,11]. In patients such as those with FPLD with severe or very severe hypertriglyceridemia, fibrates, omega-3 fatty acids (OMG-3) and occasionally niacin are first-line therapy.

Fibrates decrease TG levels by 30–50% and sometimes increase HDL-C levels in patients with hypertriglyceridemia [12]. In patients with high TG levels, LDL-C levels may increase during therapy, likely due to an increased conversion of VLDL to LDL. Side effects associated with fibrates may include elevated liver enzymes, increased CK, and hyperhomocysteinemia. Fibrates are contraindicated in patients with liver and gall bladder disease and should be used with caution in renal insufficiency [12]. Omega-3 fatty acids are used in the treatment of patients with hypertriglyceridemia. To achieve a TG reduction of 20–50%, administration of 3–4 g/d of EPA plus DHA given in multiple capsules is required [13]. As with fibrates, with the reductions of TG levels there can be increased levels of LDL-C [12]. Niacin lowers TG and increases HDL-C levels in patients with hypertriglyceridemia. At doses of 500 to 2000 mg/d, niacin lowers TG by 10–30%, increases HDL-C by 10–40%, and lowers LDL-C by 5–20% [14]. Increased risk of flushing, diarrhea, nausea, vomiting, cough, and pruritus with niacin has tended to limit its use in general practice. Moreover, when co-administered with lovastatin or simvastatin, the risk of rhabdomyolysis and abnormal liver function is increased, particularly in the elderly and in patients with diabetes, CKD, or uncontrolled hypothyroidism [15]. Background statin therapy is increasingly common in patients with moderate[1] to severe hypertriglyceridemia, however, patients with FPLD are often statin intolerant.

NAFLD is often associated with FPLD. We reported the spectrum of NAFLD associated with FPLD which appears to be more frequent than what is seen in common Type 2 diabetes and appears more severe than common forms of NAFLD [16] and very often associated with NASH. The etiology for the latter is not clear, however, the fact that a mouse model of liver specific laminopathy develops NASH in a cell –autonomous manner suggests [17]that the specific cellular defects seen in FPLD may play a role in the development of NAFLD/NASH. Triglyceride content in the liver is regulated by fatty acid uptake as well as fatty acid and VLDL production rates. Derangements in these processes, such as excessive production of fatty acids and TGs that can occur with excessive carbohydrate consumption contribute to NAFLD [18]. Patients with NAFLD compared to controls, present with an atherogenic dyslipidemic profile, characterized by increased serum levels of TGs, ApoB, VLDL-C, and LDL-C with a proportionally greater content of small dense LDL-C (sdLDL-C) [18-20]. NAFLD is also associated with aberrant nuclear receptor function and systemic

inflammation [21]. NAFLD can progress to NASH. NASH is marked by hepatocyte ballooning and liver inflammation, which may progress to scarring and irreversible damage. Macro and microscopically, NASH is characterized by lobular and/or portal inflammation, varying degrees of fibrosis, hepatocyte death and pathological angiogenesis. At its most severe, NASH can progress to cirrhosis, hepatocellular carcinoma (HCC) and liver failure. It is estimated that 20-33% NAFLD patients will progress to NASH, with about 5% ultimately progressing to cirrhosis. Cirrhosis has a reported 7- to 10-year mortality of 12-25% [22-24].

As NAFLD and NASH continue to be a growing epidemic, gemcabene's clinical and preclinical data suggest that this novel agent may provide benefit to patients with the diagnosis of NAFLD and/or NASH. As such, further development of gemcabene may help meet an unmet medical need in these patient populations.

In Phase 2 studies, gemcabene has shown TG lowering from 20 to > 50% based on dose and severity of hypertriglyceridemia and lowering in hsCRP of up to 50%. Additionally, in animal and cell based models, gemcabene studies have provided evidence demonstrating: reduction in de-novo lipogenesis, reduction in intrahepatic TG levels, modulation of inflammation and reduction of the NAFLD activity score, particularly related to hepatic ballooning, steatosis, fibrosis, and collagen accumulation. As such gemcabene may have utility in hypertriglyceridemia of FLP and ultimately in the prevention or treatment of NASH in these patients.

1.3 Risk Assessment of Gemcabene

The clinical program conducted to date has demonstrated that gemcabene is generally well tolerated. A total of 895 healthy adult volunteers and patients with various underlying conditions (including dyslipidemia, osteoarthritis, and hypertension) have been exposed to a minimum of at least one dose of gemcabene at doses ranging from 150 mg to 1500 mg once daily (QD). This includes 837 patients who received multiple doses of up to 900 mg for up to 12 weeks. This also includes 292 patients (150 patients on high-intensity) on gemcabene in combination with a statin. Safety of these patients was evaluated by adverse event monitoring, clinical laboratory assessments, electrocardiograms (ECGs), physical examinations, and vital sign assessments.

No significant drug-drug interactions have been observed with simvastatin (80 mg), atorvastatin (80 mg), or digoxin (0.25 mg). No clinically relevant effect on QTc or blood pressure has been observed.

Across all clinical studies, the majority of treatment-emergent adverse events were mild to moderate in intensity. The most common adverse events reported included headache, asthenia (feeling of weakness), nausea, dizziness, dyspepsia (upset stomach), infection, abnormal bowel movements, myalgia, and abnormal kidney function tests. Ten patients (1%) reported a treatment-emergent serious adverse event (SAE) across all previous studies. None of these SAEs were considered treatment-related. There were no deaths.

Small mean increases in serum creatinine and blood urea nitrogen (BUN) have been observed in some studies. These changes appeared within the first two to four weeks and did not appear to increase further over time. An iohexol clearance study showed that glomerular filtration rate (GFR) slightly decreased and was associated with a slight increase in serum creatinine. There was no indication of proteinuria or hematuria identified in any patient. There were no significant changes

observed in urine protein, which seems to indicate that gemcabene does not cause tubular or glomerular injury. And, the increase was reversible with all creatinine values returning to baseline within approximately two weeks of cessation of gemcabene, suggesting a vascular effect and not renal injury.

Based on a prospective analysis in a gemcabene monotherapy study (1027-04) in patients with mild-moderate hypertriglyceridemia (TG $\geq$200 mg/dL) and a retrospective meta-analysis of all studies that tested gemcabene monotherapy in patients with mild to severe hypertriglyceridemia (1027-04, 1027-14 [healthy, obese patients], and 4141001 [monotherapy arm of a study in hyperlipidemia patients +/- atorvastatin], we conclude that the 300 mg once daily (QD) dose is optimal based for gemcabene monotherapy. The 600 mg dose will also be included for the following reasons: gemcabene has a U-shaped TG dose response curve in Type IV patients and including both 300 and 600 mg may further elucidate the mechanism; and although TG lowering is mitigated at gemcabene 600 mg in HTG patients, LDL-C was significantly lowered at the 600 mg dose by a median % change of 17% (p=0.026). In addition, those studies that evaluated hsCRP showed approximately a 50% lowering at gemcabene 600 mg. Therefore, we propose including the 300 mg and 600 mg dose to assess preliminary efficacy and safety in this preliminary study of FPLD patients.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to assess the overall efficacy and safety of gemcabene (300 mg once daily given for 24 weeks; or 300 mg once daily for 12 weeks followed by 600 mg once daily for 12 weeks) in up to eight patients with FPLD and a fasting TG value ≥ 250 mg/dL and hepatic quantifiable hepatic steatosis ≥10% (as determined by magnetic resonance proton density fat fraction [MRI-PDFF]).

2.1.2 Secondary Objectives

The specific secondary objectives of this study are the following:

- To assess the effect of gemcabene on TG and other lipid and apolipoprotein parameters;
- To assess the effect on liver fat content as measured by MRI-PDFF;
- To assess the effect on hepatic fibrosis as measured by MR-elastography.
- To assess change in NAS including steatosis, lobular inflammation and hepatocyte ballooning;
- To assess the effects of gemcabene on biomarkers of inflammation;
- To assess the safety and tolerability of gemcabene 300 mg and 600 mg QD.

2.1.3 Exploratory Objectives

The exploratory objectives are the following:

- To assess changes in additional biomarkers of hepatic steatosis, lipid metabolism, obesity and diabetes;
- To assess changes in quality of life (QOL) measures.

2.2 Endpoints

2.2.1 Primary Endpoint

The primary endpoint of this study is the percent change from baseline to Week 12 in fasting serum TG.

2.2.2 Secondary Efficacy Endpoints

The secondary endpoints are as follows:

- Change and percent change in fasting serum TG from baseline to average of Weeks 6 and 12, and Week 24 and change in fasting serum TG from baseline to Week 12;
- Change and percent change in liver fat content as determined by MRI-PDFF from baseline to Week 12 and Week 24;

- Change and percent change in liver fibrosis as determined by MR-elastography from baseline to Week 12 and Week 24;
- Change and percent change in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) (ultracentrifugation), HDL-C, apolipoprotein B (apo B), ApoA-1, ApoA-II, ApoA-V from baseline to Weeks 12 and 24;
- Change and percent change in high-sensitivity C-reactive protein (hsCRP), fibrinogen, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) from baseline to Weeks 12 and 24.

2.2.3 Safety Measures

The safety variables include adverse events, safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) with particular attention to hepatic (e.g., ALT/AST, bilirubin, alkaline phosphatase, GGT, renal (e.g., blood urea nitrogen [BUN], serum creatinine, protein:creatinine ratio, albumin/creatinine ratio, urinalysis sediments, pH, electrolytes), and skeletal muscle toxicities (i.e., creatine kinase), ketone bodies, 12-lead electrocardiograms (ECGs), physical examinations, and vital signs.

2.2.4 Exploratory Endpoints

The exploratory efficacy endpoints are as follows:

- Change and percent change in biomarkers of hepatic steatosis including AST/ALT ratio; γ-glutamyl transpeptidase, (GGT); alkaline phosphatase; international normalized ratio (INR), albumin, total bilirubin from baseline to Week 12 and Week 24;
- Liver mRNA levels which may include *de novo* cholesterol synthesis and lipogenesis, inflammation, LDL receptor, β-oxidation, and sulfatase from baseline to Week 24;
- Change and percent change in leptin, adiponectin and fasting insulin levels, fasting plasma glucose (FPG), and hemoglobin A1c (HbA1c), non-high-density lipoprotein cholesterol (non-HDL C), very low density lipoprotein cholesterol (VLDL-C), ApoC-II, ApoC-III, ApoE and Lp(a) from baseline to Week 12 and Week 24;
- Change and percent change in interleukin-6 (IL-6), interleukin 1β (IL-1β), angiopoietin like 4 transpeptidase (ANGPTL4), angiopoietin like 3 transpeptidase (ANGPTL3), fibrinogen, and serum amyloid A (SAA), from baseline to Weeks 12 and 24.
- Change and percent change in NAS (NAFLD activity score)[23] including steatosis, lobular inflammation and hepatocyte ballooning from baseline to Week 24;
- Change and percent change in QOL measures including visual analog scale (VAS) of pain, short form-36 (SF-36), and Michigan Body Map from baseline to Weeks 12 and 24.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

Although this is a pilot IND study, measures must be put in place to stabilize TG measures at baseline and concomitant TG-lowering therapies to ensure the collection of meaningful data during study conduct. The study will consist of a six week Wash Out Period, up to a 28-day Screening Period, a 24 week Treatment Period, and a follow-on safety assessment four weeks post final dose. Below is a general description of each Period of the study.

Pre-Screening Visit/Wash-Out Period

A Pre-Screening Visit followed by a Wash-Out Period will be required for eligible patients taking fibrates, niacin ≥250 mg/day or over-the-counter fish oil or other products containing omega-3 fatty acids (OMG-3), or thiazolidinediones (TZDs). For patients requiring a Wash-Out Period, the Pre-Screening Visit will be their first study visit and will occur prior to the Screening Visit based on the duration of the Wash-Out Period required.

Patients currently taking fibrates, niacin ≥250 mg/day, prescription or over-the-counter fish oil or other products containing OMG-3, or TZDs must be able to safely discontinue therapy at screening. The Wash-Out Period will be six weeks. If patients are on metreleptin for investigational use, they should be washed out for four months and their leptin level must have returned to pre-metreleptin treatment state, which is indirect evidence that any binding antibodies may have decayed as well.

Screening Period

All eligible patients will participate in the Screening Visit up to 28 days prior to Day 1. For eligible patients taking stable, allowable, lipid-lowering therapy (statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, or other herbal products or dietary supplements with potential lipid-altering effects) for greater than six weeks and who do not require a Wash-Out Period, the Screening Visit will be their first study visit.

At the end of the two-to four-week diet and lifestyle stabilization and TG qualifying period, eligible patients must have a fasting TG ≥250 mg/dL prior to their MRI-PDFF performed at Visit S2. The TG level for qualification will be based on Visit S1. If a patient's TG value from Visit S1 falls outside the required range for entry into the study, one additional sample for fasting TG measurement can be collected between Visits S1 and S2.

During this Screening Period, potential patients must have hepatic steatosis of 10% based on the core imaging lab assessment of liver fat content (MRI-PDFF) to be eligible for enrollment on Day 1 (Visit T1). If the core imaging lab assessment of liver fat content is below the minimum range outlined in the protocol the patient will be ineligible and will not be eligible for re-screening. A determination of hepatic fibrosis (MR elastography) will also be performed during Screening.

Patients meeting screening criteria including TG and 10% liver fat will be offered an optional liver biopsy performed for the assessment of a baseline NAS.

Open-Label Randomized Treatment Period

After confirmation of qualifying fasting TG values and MRI-PDFF confirmed hepatic steatosis ≥10%, eligible patients will have a fasting liver biopsy performed, if they opt in, and enter the treatment phase to receive 300 mg gemcabene daily for 12 weeks starting on Day 1/Visit T1. Up to eight patients will be treated. After 12 weeks at visit T4, patients will be randomized 1:1 according to a pre-generated randomization code to the remaining 12 -week treatment period:

- Group 1: Gemcabene 300 mg QD for 12-24 weeks
- Group 2: Gemcabene 600 mg QD for 12-24 weeks

The primary evaluation of TG efficacy will be after 12 weeks of treatment. The primary evaluation for the secondary parameters of liver fat (MRI-PDFF) and NAS (histology) will be at 24 weeks.

Safety Follow-Up Assessment 4 Weeks Post-Final Dose

The Follow-up telephone call will occur four weeks (±3 days) after the last dose of study drug.

3.2 Study Indication

Treatment with gemcabene is indicated as an adjunct to diet to reduce TG levels and indicators of nonalcoholic fatty liver disease (NAFLD) in adult patients with Familial Partial Lipodystrophy Disease (FPLD).

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients who meet all the following criteria will be eligible to participate in the study:

1. Male or female ≥18 years of age at time of consent with written and signed informed consent (by patient or legal guardian) prior to any study-specific procedure;
2. Clinical diagnosis of lipodystrophy based on deficiency of subcutaneous body fat in a partial fashion assessed by physical examination, and at least one of the following MAJOR criterion (below):
   - Low skinfold thickness in anterior thigh by caliper measurement: men (≤10 mm) and women (≤22 mm); OR
   - Historic genetic diagnosis of Familial Partial Lipodystrophy Disease (e.g. mutations in LMNA, PPAR-γ, AKT2, or PLIN1 genes) as supported by source documentation.
3. Hepatic steatosis (>10% – Stage 2 or 3) as demonstrated by MRI-PDFF;
4. Alcohol intake of less than 20 g per day in females and 30 g per day in males;
5. Mean fasting TG value ≥250 mg/dL mg/dL at Screening;
6. Background lipid lowering therapy (statins, ezetimibe, PCSK9 inhibitors or other herbal products or dietary supplements with potential lipid-altering effects) must be stable for at least six weeks prior to the Screening Visit (S1);
7. Female patients must not be pregnant or lactating. Women of child-bearing potential must have a negative serum pregnancy test at the Screening Visit and negative urine dipstick on Day 1 prior to dosing in order to qualify for the study. Women who are surgically sterile or are clinically confirmed to be post-menopausal (i.e., documented amenorrhea for ≥1 year in the absence of other biological or physiological causes) are not considered to be of child-bearing potential; and
   - Women of child-bearing potential must agree to use acceptable methods of contraception throughout the duration of the study and for 30 days after the last dose of study drug. For this study, double-barrier contraception is required such as condom or occlusive cap (e.g. diaphragm or cervical/vault caps) plus spermicidal agent (e.g. foam, gel, film, cream, suppository).
   - Male patients must agree to use contraception by means of a condom and may not donate sperm throughout the duration of the study and for eight days after the last dose of study drug.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Weight <50 kg;
2. Body mass index (BMI) >45 kg/m²;

3. Current, or history of, autoimmune diseases;
4. Laboratory or other histologic findings highly suggestive of liver disease due to causes other than non-alcoholic steatohepatitis, such as chronic viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, biliary obstruction or genetic liver diseases such as Wilson's disease, hemochromatosis or alpha-1-antitrypsin deficiency;
    - Treatment with drugs associated with steatohepatitis, e.g., corticosteroids, high dose estrogens, methotrexate, amiodarone, tamoxifen, valproic acid, sulfasalazine, or oxacillin for more than two weeks in the six months prior to the study;
    - Abnormal liver function test at screening (aspartate aminotransferase or alanine aminotransferase > 3x ULN, total bilirubin or alkaline phosphatase greater than the ULN; Subjects with a history of Gilbert's syndrome may be included if both direct bilirubin and the reticulocyte count do not exceed the ULN [reflexive direct bilirubin testing will be used to confirm Gilbert's syndrome]);
    - Decompensated liver disease as evidenced by clinical features of hepatic failure (variceal bleeding, ascites, hepatic encephalopathy etc.) and laboratory investigations (prolonged prothrombin time with INR > 1.3 x ULN, platelet count < 150,000 cells/mm^3, hypoalbuminemia with serum albumin less than 3.0 g/dL, direct bilirubin > 1.3 mg/dL, abnormal alkaline phosphatase) or presence of esophageal varices etc.;
    - Evidence of hepatocellular carcinoma: alpha-fetoprotein levels greater than 200 ng/ml and/or liver mass on imaging study suggestive of liver cancer;
    - Use of drugs which can potentially decrease hepatic steatosis during previous three months; ursodeoxycholic acid, thiazolidinediones, high-dose vitamin E, betaine, acetylcysteine and choline;
5. Other significant systemic or major illnesses, such as congestive heart failure (NYHA Class III or IV), cerebrovascular disease, respiratory failure, renal insufficiency, acute pancreatitis (within four weeks of Screening Visit), organ transplantation, serious psychiatric disease, and malignancy, that could interfere with the trial and adequate follow up;
    - Myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, or other major cardiovascular events resulting in hospitalization within three months of the Screening Visit. Patients with adequately treated stable angina, per Investigator assessment, may be included;
    - Uncontrolled cardiac arrhythmia or prolonged QT on the Screening Visit or Day 1 prior to dosing ECG (QTcF > 450 msec for men and > 470 msec for women) or known family history of prolonged QT or unexplained sudden cardiac death;
    - Uncontrolled hypertension, defined as sitting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg, and confirmed by repeat measurement;
    - Moderate to severe renal insufficiency defined as an estimated GFR < 60 mL/min/1.73m^2 (calculated using The Chronic Kidney Disease Epidemiology Collaboration equation) at the Pre-Screening Visit or the Screening Visit;

- Hematocrit of less than 30%;
- Type 1 diabetes mellitus or uncontrolled diabetes mellitus (hemoglobin A1c [HbA1c] value ≥9.5% based on results from the Pre-Screening Visit or the Screening Visit);

6. Use of a fibrate, niacin ≥250 mg/day, prescription or over-the-counter fish oil or other products containing OMG-3, or TZDs within the last six weeks prior to Screening;
7. If patients are on metreleptin for investigational use, they should be washed out for four months and their leptin level must have returned to pre-metreleptin treatment state which is indirect evidence that any binding antibodies may have decayed as well;
8. Use of strong UGT inhibitors: amitriptyline, atazanavir, deoxyschizandrin, diclofenac, efavirenz, erlotinib, hecogenin, niflumic acid, nilotinib, probenecid, and valproic acid;
9. Patients with hypersensitivity to or have a history of significant adverse reactions to fibrates;
10. Patients on potent CYP3A4 inhibitors such as itraconazole or a macrolide antibiotic;
11. Previously treated with gemcabene; participation in another clinical study of an investigational agent or device concurrently or within one month prior to the Screening Visit, or use of an investigational agent within one month or five half-lives (if known), whichever is longer, prior to the Screening Visit;
12. Or any other finding which, in the opinion of the Investigator, would compromise the patient's safety or participation in the study.

4.3 Withdrawal Criteria

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any SAE, clinically significant adverse event, severe laboratory abnormality, concomitant illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Pregnancy;
- Requirement of prohibited concomitant medication
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination (ET) Visit. The reason for patient withdrawal must be documented in the Case Report Form (CRF) and on the source document(s).

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

Withdrawn patients will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

Up to eight patients will enter the treatment phase to receive 300 mg gemcabene daily for 12 weeks starting on Day 1/Visit T1. After 12 weeks of treatment, at visit T4, patients will be randomized 1:1 according to a pre-generated randomization code to either of the following groups:

Group 1: Gemcabene 300 mg QD for weeks 12-24

Group 2: Gemcabene 600 mg QD for weeks 12-24

5.2 Dose Rationale

Based on a prospective analysis in a gemcabene monotherapy study (1027-04) in patients with mild-moderate hypertriglyceridemia (TG ≥200 mg/dL) and a retrospective meta-analysis of all studies that tested gemcabene monotherapy in patients with mild to severe hypertriglyceridemia (1027-04, 1027-14 [healthy, obese patients], and 4141001 [monotherapy arm of a study in hyperlipidemia patients +/- atorvastatin], we conclude that the 300 mg once daily (QD) dose is optimal. The 600 mg dose will also be included for the following reasons: gemcabene has a U-shaped TG dose response curve in Type IV patients and including both 300 and 600 mg may further elucidate the mechanism; and although TG lowering is mitigated at gemcabene 600 mg in HTG patients, LDL-C was significantly lowered at the 600 mg dose by a median % change of 17% (p=0.026). In addition, those studies that evaluated hsCRP showed approximately a 50% lowering at gemcabene 600 mg. Therefore, we propose including the 300 mg and 600 mg dose to assess preliminary efficacy and safety in this study of FPLD patients.

Study 1027-04

In a pre-specified analysis in patients with TG ≥200 mg/dL (Study 1027-04) gemcabene lowered TG by a median % change at 12 weeks of by 27% ($p < 0.05$), 39% ($p < 0.01$), 13% ($p=0.623$), and 9% ($p=0.952$) at the 150 mg, 300 mg, 600 mg, and 900 mg doses, respectively, compared to a 5% lowering for placebo. The dose response curve was U-shaped with the maximum effect at 300 mg. There was a correlative decrease in ApoC-III of 24% ($p <0.05$) and 31% ($p <0.01$) at the 150mg and 300 mg doses, respectively. There was also a statistically significant lowering of ApoE by 37% ($p <0.01$) at 300 mg.

Similar to OMG-3 compounds and fibrates, gemcabene increases LDL-C in patients with isolated hypertriglyceridemia (Type IV) when TG levels are lowered. Small non-significant increases in LDL-C at gemcabene 150 mg and 300 mg and significant lowering in LDL-C of 17% ($p=0.026$) and 23% ($p <0.001$) at gemcabene 600 mg and 900 mg, respectively; compared to an increase of 0.4% on placebo were observed. It is hypothesized that in this population treated patients are shifting from a pattern A to pattern B profile, whereby larger less atherogenic LDL particles are being formed. This is supported by a moderate non-significant decrease in ApoB across all doses.

Retrospective Meta-Analysis

A retrospective meta-analysis of the effect of gemcabene monotherapy on TG in patients exposed to drug for at least 50 days included studies 1027-04 (low HDL), 1027-14 (healthy obese) and

4141001 (hypercholesterolemic) all of which enrolled some patients with TG ≥200 mg/dL. The effect of gemcabene in patients on background statin was also analyzed (1027-18).

The sub-cut of gemcabene monotherapy patients with TG ≥200 mg/dL had a median % lowering in TG of 25% (p=0.0192) and 32% (p=0.0051) for gemcabene 150 mg (n=22) and 300 mg (n=27), respectively, compared to a lowering of 3% for placebo (n=31). No significant differences were observed in TG levels at the 600 mg or 900 mg doses versus placebo. Gemcabene *in combination with statin* had a median % lowering in TG similar to monotherapy: 38% (p=0.0067) for gemcabene 300 mg + statin (n=23), 46% (p=0.0028) for gemcabene 600mg + statin (n=13) compared to a lowering of 19% with statin alone (n=26).

5.3 Randomization and Blinding

Patients who have completed the Screening Visit and meet all inclusion and none of exclusion criteria will begin treatment on Study Day 1. At week 12 (Visit T4) subjects will be randomized to either 300 mg gemcabene or 600 mg gemcabene for the remiaing 12 weeks of study. Randomized treatment assignment and randomization numbers will be assigned by paper. Following randomization, study drug will be dispensed in an open-label manner.

5.4 Drug Supplies

5.4.1 Study Drug Identification

CAS Registry Number	209789-08-2 – parent 183293-82-5
Chemical Class	Anti-hypercholesterolemic
Chemical Name	6,6'-oxybis (2,2-dimethylhexanoic acid) monocalcium salt or 6-(5-carboxy-5-methyl-hexyloxy)-2,2-dimethylhexanoic acid calcium
USAN Name	Gemcabene calcium
Parent Compound	6,6'-oxybis (2,2-dimethylhexanoic acid) or 6-(5-carboxy-5-methyl-hexyloxy)-2,2-dimethylhexanoic acid
USAN Name	Gemcabene
Molecular Formula	Chemical Formula Calcium Salt: $C_{16}H_{28}O_5$•Ca Chemical Formula Parent: $C_{16}H_{30}O_5$
Relative Molecular Mass	Molecular Weight Calcium Salt: 340.48 Molecular Weight Parent: 302.41

Formulation/amount	Tablets/300 mg
Manufacturer (drug substance)	Corden Pharma Switzerland
Manufacturer (drug product)	Catalent Pharma Solutions
Storage Requirements	Room temperature (15-30°C) in a secured location (locked) with no access for unauthorized personnel.

5.4.2 Formulation and Packaging

The drug product for oral administration is an immediate-release tablet containing the equivalent of 300 mg of gemcabene as its calcium salt, in a formulation comprising the following inactive ingredients: lactose monohydrate, hydroxypropyl cellulose, croscarmellose sodium magnesium stearate. The tablets are film coated with a blend of simethicone 30% emulsion and Opadry White YS 1-7040.

Study drug will be prepared as a 30-day supply in bottles and dispensed based on the assigned treatment group. In accordance with 21 CFR §312.6 the packaging will bear a label with the statement "Caution: New Drug – Limited by Federal (or United States) law to investigational use."

Subjects will be instructed to take one (1- 300 mg tab) or two (2- 300 mg tabs) per day, based on treatment assignment.

5.4.3 Study Drug Preparation and Dispensing

Study drug will be administered at the site on clinic visit days. Patients will self-dose at all other times during the Treatment Period. The Investigator or designee will provide patients with sufficient study drug until the next scheduled study visit.

5.4.4 Study Drug Administration

Patients will be instructed to take study drug at the same time in the morning either with or without food and with water. Missed doses will be documented. If a patient misses a dose, two doses should not be taken the following day.

5.4.5 Treatment Compliance

Patients will be instructed to take study drug daily according to the protocol and return used and unused packaging to the site at each subsequent study visit.

Compliance with administration of study drug will be assessed at each study visit post-enrollment during the Treatment Period and at the Early Termination Visit, if applicable, and recorded on the appropriate CRF and the drug accountability log.

The Investigator or designee will remind patients at each visit of the importance of following the protocol-defined schedule for taking study drug. Reasons for not following the study drug

administration schedule as described in the protocol will be clearly recorded in the source documents.

5.4.6 Storage and Accountability

The study drug will be stored at room temperature (15-30°C) in a secured location (locked) with access restricted to authorized personnel only. The storage temperature will be monitored and recorded.

Upon receipt of study drug, the Investigator or designee will conduct a complete inventory of all study drug and ensure no damage occurred during shipment.

The Investigator will maintain adequate records documenting the receipt, use, loss, or other disposition of study drug. Drug accountability logs will identify the study drug code number and account for the disposition on a patient-by-patient basis, including specific dates and quantities. The drug accountability logs will be signed by the individual who dispenses the study drug and copies will be provided to the Sponsor and Gemphire Therapeutics.

All used and unused supplies will be appropriately inventoried and verified by the Clinical Research Associate (CRA).

Unused study drug may be destroyed at the sites according to their Standard Operating Procedures (SOPs).

5.5 Prior and Concomitant Medications and/or Procedures

5.5.1 Permitted Medications and/or Procedures

Patients are required to be on a stable, low-fat, low-cholesterol diet. Patients should remain on previously prescribed background lipid-lowering therapy for the duration of the study, if started at least six weeks prior to the Screening visit. It is important that background lipid-lowering is stable with the same dose taken at the same time each day. FPLD patients who receive pharmacologic treatment for their disease or any other chronic medical condition (i.e., diabetes) must be on a stable regimen for three months prior to signing informed consent and should remain on this regimen, if possible, during study conduct.

5.5.2 Excluded Medications and/or Procedures

Patients are not permitted to receive treatment with a fibrate lipid-regulating agent, niacin ≥250 mg/day, prescription or over-the-counter fish oil or other products containing OMG-3, or a TZD for at least six weeks prior to the Screening Visit.

Patients are not permitted the use of tamoxifen, estrogens or progestins that have not been stable for greater than four weeks prior to Visit 1, nor permitted the use of oral or injected corticosteroids or anabolic steroids. If patients are on metreleptin for investigational use, they should be washed out for four months.

Patients are not permitted the use of strong UGT inhibitors: amitriptyline, atazanavir, deoxyschizandrin, diclofenac, efavirenz, erlotinib, hecogenin, niflumic acid, nilotinib, probenecid, and valproic acid.

5.5.3 Restrictions and Dietary Guidelines

It is important that patients are instructed to not undertake any form of strenuous physical activity for at least 24 hours prior to blood testing.

Patients are restricted from using alcohol 48 hours prior to study visits. Patients must not drink more than two units of alcohol per day. A unit of alcohol is defined as 12 ounces (350 ml) of beer, 5 ounces (150 ml) of wine, or 1.5 ounces (45 ml) of 80-proof alcohol for mixed drinks.

Clinic visit assessments that require a patient to fast will be defined as no food or caloric beverage for at least eight hours prior to sample collection. Patients will be permitted to have water, tea or black coffee.

Study drug should be taken at the same time in the morning either with or without food.

Patients will maintain a stable, heart-healthy diet (as self-reported) throughout the study.

5.5.4 Documentation of Prior and Concomitant Medication Use

A concomitant medication is any treatment including nutritional supplements, vitamins, or over-the-counter medications received by or prescribed to the patient concomitantly to the study, from the time of informed consent to the Follow-up Visit or the ET Visit, if applicable.

The Investigator should record the use of all concomitant medications taken during the study, both prescribed and over the counter, in the CRF and the source document. This includes medications used on a chronic and as needed basis. Patients should be discouraged from starting any new medication, both prescribed and over the counter, without consulting the Investigator, unless the new medication is required for an emergency.

6 STUDY PROCEDURES

An overview of the visits is below with a tabular listing of the Schedule of Procedures located in Appendix A. Assessments that require a patient to fast will be defined as no food or caloric beverage (tea and black coffee are allowed) for at least eight hours prior to sample collection. Patients will be permitted to have water.

6.1 Informed Consent

Written informed consent for the study will be obtained from all patients before any protocol-specific procedures are performed. See Section 12.3 for details on informed consent.

6.2 Pre-Screening Visit

Only patients with a history within the past year of TG ≥ 200 mg/dL on current TG-lowering therapy and requiring a Wash-Out Period will participate in the Pre-Screening Visit.

A six-week Wash-Out Period will be required for eligible patients taking fibrates, niacin ≥250 mg/day, prescription or over-the-counter fish oil or other products containing OMG-3, or TZDs. If patients are on metreleptin for investigational use, they should be washed out for four months and their leptin level must have returned to pre-metreleptin treatment state which is indirect evidence that any binding antibodies may have decayed as well.

Refer to Appendix A for procedures that will be performed at the Pre-Screening Visit.

6.3 Screening Visits

All eligible patients will participate in the Screening Period up to 28 days prior to Day 1. For eligible patients taking stable allowable, lipid-lowering therapy (statins, ezetimibe, niacin, PCSK9 inhibitors, or other herbal products or dietary supplements with potential lipid-altering effects) for greater than six weeks and who do not require a Wash-Out Period, the Screening Visit will be their first study visit. To qualify for enrollment in the treatment period, the fasting TG measurement at Visit S1 must be ≥250 mg/dL (2.83 mmol/L). If a patient's TG value from S1 falls outside the required range for entry into the study, one additional sample for fasting TG measurement can be collected prior to S2.

At Visit S2 potential patients must have hepatic steatosis ≥10% based on the core imaging lab assessment of liver fat content (MRI-PDFF) to be eligible for enrollment on Day 1 (Visit T1). If the core imaging lab assessment of liver fat content is below the minimum range outlined in the protocol the patient will be ineligible and will not be eligible for re-screening. A determination of hepatic fibrosis (MR elastography) will also be performed at this visit.

Patients meeting screening criteria including TG and 10% liver fat will be offered an optional liver biopsy performed for the assessment of a baseline NAS. If all of the inclusion criteria (Section 4.1) are met and the patient has none of the exclusion criteria (Section 4.2) the patient may be randomized into the 12-week treatment period.

6.3.1 Screening Visit S1 (up to Day -28)

Only patients with a history within the past year of TGs ≥250 mg/dL and NOT requiring wash-out from fibrates, prescription or over-the-counter fish oil or other products containing OMG-3, niacin ≥250 mg/day or TZDs may participate in Screening Visit 1. Patients may be receiving statins, ezetimibe, PCSK9 inhibitors, or other herbal products or dietary supplements with potential lipid-altering effects only if therapy is stable for greater than six weeks prior to Screening Visit 1.

For patients determined as ineligible based on TG levels <250 mg/dL at Visit S1 ONLY a fasting lipid panel for the measurement of TGs can be reassessed at an interim visit between Visits S1 and S2.

For patients who required a wash-out period and completed the Pre-Screening Visit, the following Screening Visit procedures will **not** be repeated: informed consent, full physical examination, height, TSH, and serology (HBV, HCV, and HIV). Updates, as needed, will be made to medical/surgical history, demographics, and concomitant medications.

Refer to Appendix A for procedures that will be performed at the Screening Visit S1 (up to Day -28).

6.3.2 Screening Visit S2

Patients with a qualifying TG level ≥250 mg/dL will have an assessment of liver fat content to determine eligibility as measured by MRI-PDFF. If this core imaging lab assessment of liver fat is below 10% the patient will be ineligible for enrollment and will not be eligible for re-screening. A determination of hepatic fibrosis (MR elastography) will also be performed at this visit.

Refer to Appendix A for all procedures that will be performed at the Screening Visit S2.

6.4 Treatment Period (Visit T1 through Visit T7)

6.4.1 Visit T1 (Study Day 1)

Patients meeting screening criteria including TG and 10% liver fat will be offered an optional liver biopsy, which will be performed for the assessment of a baseline NAFLD Activity Score (NAS). If patients opt-out of the liver biopsy, they can still move to the treatment phase.

Open-label, Treatment Period: After confirmation of qualifying fasting TG values and MRI-PDFF confirmed hepatic steatosis ≥10%, eligible patients will have a fasting liver biopsy performed if they opt in and move to treatment phase with 300 mg daily for 12 weeks starting on Day 1/Visit T1. Up to eight patients will be treated.

The T1 visit may occur over several days, but no more than 7 days.

Refer to Appendix A for procedures that will be performed **pre-dose** at Visit T1 (Day 1).

6.4.2 Visit T2 (Week 4)

Refer to Appendix A for procedures that will be performed at Visit T2 (Week 4 ±3 days).

6.4.3 Visit T3 (Week 8)

Refer to Appendix A for procedures that will be performed at Visit T3 (Week 8 ±3 days).

6.4.4 Visit T4 (Week 12) Randomized Treatment Period

Refer to Appendix A for procedures that will be performed at Visit T4 (Week 12 ±3 days). After 12 weeks at visit T4, patients will be randomized 1:1 according to a pre-generated randomization code to the remaining 12 -week treatment period in a 1:1 ratio to one of the following:

- Group 1: Gemcabene 300 mg QD for 12-24 weeks

  Group 2: Gemcabene 600 mg QD for 12-24 weeks

6.4.5 Visit T5 (Week 16)

Refer to Appendix A for procedures that will be performed at Visit T5 (Week 16 ±3days).

6.4.6 Visit T6 (Week 20)

Refer to Appendix A for procedures that will be performed at Visit T6 (Week 20±3 days).

6.4.7 Visit T7 (Week 24)

Refer to Appendix A for procedures that will be performed at Visit T7 (Week 24±3days)

6.5 Follow-up Visit 8 (Week 28; Telephone Call four weeks post-dose)

The Follow-up Visit will be conducted as a telephone call four weeks (±3 days) after the last dose of study drug, during which it will be assessed how the patient is doing with a body systems review, unless the patient requires a site visit due to an abnormal result at Week 24 (or the ET Visit, if applicable) or an ongoing treatment-related adverse event.

Refer to Appendix A for procedures that will be performed at the Follow-up Visit (Week 28 ±3 days) if done in person due to an adverse event.

6.6 Early Termination Visit and Withdrawal Procedures

For patients who are withdrawn from the study prior to completion, refer to Appendix A for procedures that will be performed at the ET Visit.

7 EFFICACY ASSESSMENTS

7.1 Biomarker Assessments

The following efficacy assessments will be measured in order to obtain the primary, secondary, and exploratory endpoints. Refer to Appendix A for procedures that will be performed at specific timepoints.

- Fasting lipid panel which includes: TG, TC, HDL-C, non-HDL-C, VLDL-C, LDL-C (ultracentrifugation);
- Fasting Apo B, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, and ApoE;
- hsCRP, SAA, IL-6, fibrinogen, IL-1β, ANGPTL4, and ANGPTL3;
- Fasting insulin levels, FPG, HbA1c, leptin, adiponectin;
- Change and percent change in biomarkers of hepatic steatosis including GGT; Alk Phos; AST and ALT ratio, AST/ALT ratio, INR, albumin, bilirubin from baseline to various timepoints; and
- Change and percent change in liver mRNA levels which may include denovo cholesterol synthesis and lipogenesis, inflammation, LDL receptor, β-oxidation, and sulfatase from baseline to Week 24;
-

7.2 Evaluation of NAFLD and NASH

7.2.1 Imaging and liver biopsy

The magnetic resonance imaging–estimated proton density fat fraction (MRI-PDFF) is a novel imaging-based biomarker that allows fat mapping of the entire liver and is independent of the scanner's manufacturer and magnet strength. MRI-PDFF is emerging as the leading biomarker for assessing treatment response in NASH trials to monitor longitudinal changes in hepatic fat [25,26].

MRI-PDFF is measured with advanced MRI techniques that minimize or correct the confounding factors (T1 bias, T2* bias, and multifrequency interference effects of fat and eddy currents) that corrupt fat fraction estimations with conventional MRI-by a previously described and validated protocol [27-30]. The protocol uses a gradient echo sequence with a low flip angle to minimize T1 bias, and it acquires multiple echoes in which the multiple spectral peaks of lipid at and water interfere with respect to each other. Once data are acquired at each echo of the echo times, they pass to a fitting algorithm that estimates and corrects T2* effects, models the fat signal, and estimates fat and water proton densities; then, the fat content is calculated [31,32].

MRI-estimated PDFF has been validated against MRS as well as liver biopsy histological data. [31,33,34]. Hepatic fat quantification via MRI-PDFF has been utilized in NASH clinical trials for quantitative fat assessment [25,29,35-37].

Based on the correlations to biopsy, the ease of conduct, the extensive availability of MRI-PDFF this is the imaging technique that will be utilized in this pilot study of FPLD.

MR-elastography will also be performed to assess tissue stiffness which has been shown to be associated with increased hepatic fibrosis[42].

Hepatic biopsy proven disease is the gold standard for diagnosis of NAFLD and NASH and for evaluation of treatment [38,39]. However, hepatic biopsy has serious procedural related risks, e.g. bleeding, perforation and death, and consequently is not appropriate for frequent routine evaluation and follow-up in patients in the clinical setting.

Although fat accumulation is generally considered diffuse in NAFLD and NASH, the distribution is non-uniform, which means any type of assessment that has limited spatial sampling may have high inter- and intra- observer variability [40-42]. Therefore, there is still the need for continued development of surrogates (i.e., MRI-PDFF) for early and mid-stage clinical studies of potential therapies, as well as for following the treatment response in the clinical setting.

A determination of NAS (NAFLD activity score) including steatosis, lobular inflammation and hepatocyte ballooning will be calculated from the liver biopsy if patients opted in for the liver biopsy. In addition, markers of mechanism and effect will be assessed including syndecan.

8 RISK ASSESSMENT

8.1 Known Potential Risks

The safety and efficacy profile of gemcabene has been developed through 18 Phase 1 and 2 studies including 1278 healthy volunteers and patients.

Common adverse events include:

- Headaches
- Asthenia (feeling of weakness)
- Nausea
- Dizziness
- Dyspepsia
- Abnormal bowel movements
- Myalgia (muscle pain)
- Increased BUN
- Increased creatinine

Identified and Potential Important Risks:

Based on the non-clinical and clinical safety data collected, important potential risks are liver findings, hemoglobin decrease, BUN and creatinine increase and myalgia. Importantly, only one patient had a transaminase elevation >3x ULN after receiving gemcabene 600 mg and atorvastatin 80 mg. While hemoglobin decrease was seen in non-clinical toxicity studies, only small decreases in hemoglobin have been observed clinically and were also seen with placebo (not statistically significant). Small increases in creatinine and BUN were observed in clinical studies with gemcabene. The increases appeared within the first two-to-four weeks of treatment and did not worsen over time.

Other risks:

- There is a possibility of rhabdomyolysis when combined with a statin.
- Patients with a hypersensitivity to or who have a history of significant adverse reactions to any fibrate lipid lower agents should avoid gemcabene.
- Patients on potent CYP 3A4 inhibitors such as itraconazole or a macrolide antibiotic should be excluded.
- Based on non-clinical studies in rats, gemcabene should not be administered to pregnant women or women of childbearing potential not using effective methods to prevent pregnancy.
- Gemcabene tests for carcinogenic activity are under review by the FDA with additional data requested for review prior to the initiation of studies greater than 6 months.

8.2 Risks from the procedures in the protocol:

Procedures in this protocol include 1) blood draws; 2) MRI; 3) IV placement for repeated blood draws; and 4) liver biopsy.

8.3 Known Potential Benefits:

Three Phase 2 studies have demonstrated that gemcabene is efficacious in reducing TGs in hypertriglyceridemic patients and LDL-C in hypercholesterolemic patients. As many FPLD patients (and patients with NAFLD) have high TGs and may have high LDL-C, this is a potential benefit for the participants.

Gemcabene has also been demonstrated to reduce ApoB and hsCRP, both associated with cardiovascular disease risk. This is also a potential benefit to the participants. Within the study, participants will benefit from receiving lifestyle counseling. They will also receive regular assessments of their liver disease including labs (ALT, AST and GGT) and MRI (hepatic steatosis).

Long range benefits could include satisfaction from contributing to development of treatments for FPLD and FPLD with NAFLD.

8.4 Assessment of Potential Risks and Benefits

The rationale for the necessity of exposing patients to the risks of participating in this study is that medications for FPLD are urgently needed.

The value of the information to be gained outweighs the risks, because the risks are minimal and the information collected could be significantly valuable for the FPLD population. Patients in the study will benefit from receiving standard of care lifestyle counseling and from state of the art measurements of their liver disease.

9 SAFETY ASSESSMENTS

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate CRF.

Adverse events, which include abnormal and clinically significant clinical laboratory test variables, will be monitored and documented from the time of first dose of study drug (Study Day 1) until study participation is complete (the Follow-up Visit). Patients should be instructed to report any adverse event that they experience to the Investigator. Beginning with the signing of the informed consent until the time of the first dose of study drug (Study Day 1), investigators should make updates to medical history and record any pre-existing medical condition or signs or symptoms that changes in severity, frequency, or seriousness in the medical history. Serious adverse events that occur prior to the first dose of study drug (Study Day 1) should be reported as an update to medical history as well as be reported on the appropriate adverse event CRF. Beginning with the first dose of study drug (Study Day 1), investigators should make an assessment for adverse events at each visit and record all adverse events, non-serious and serious, on the appropriate adverse event CRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the CRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure. Concomitant procedures should be recorded as such on the appropriate CRF.

Any medical condition already present prior to the patient taking the first dose of study drug (Study Day 1) should be reported in the medical history. Any SAEs occurring prior to the first dose of study drug (Study Day 1) should be reported as an update to medical history as well as an adverse event. Any pre-existing medical condition or signs or symptoms that changes in severity, frequency, or seriousness after the patient takes the first dose of study drug (Study Day 1) and through the Follow-up Visit should be reported as an adverse event.

Clinically significant abnormal laboratory values or other examinations (e.g., ECG) that are detected at the time of the first dose of study drug (Study Day 1) and worsen during the study should be reported as adverse events. An abnormal laboratory result that is not verified by repeat testing does not necessitate reporting as an adverse event. The Investigator will exercise his or her medical, scientific, and clinical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal,

stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

9.1.1 Adverse (Drug) Reaction

For adverse events with a causal relationship to study drug, follow-up by the Investigator will be required until the event or its sequelae resolve or stabilize to a level acceptable to the Investigator.

9.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (see Investigator's Brochure). For gemcabene, the reference safety information is included in Sections 8.4 and 10 of the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

9.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of Yes or No, as defined below.

Assessment of Severity:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality Assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (unlikely related, unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (e.g., medical history, concomitant drugs, therapies, and complications) is suspected.

Yes (possibly related, related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (e.g., medical history, concomitant drugs, therapies, and complications) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration -

The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant diseases (medical history) -

Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug -

The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug -

Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses -

The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PKs of the study drug -

The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

9.2 Specific Safety Measures

The safety parameters will be reviewed every 3 months by an Independent Safety Monitor who will be Dr. James Shayman, a professor in the Department of Medicine, Division of Nephrology and Pharmacology at the University of Michigan. Dr. Shayman is an experienced clinical investigator and also an inventor of new drugs that have gained FDA approval.

9.2.1 Hemoglobin decrease

For a hemoglobin decrease of >1.5 g/dL from baseline during the study, repeat hematology studies and reflexive evaluation of reticulocyte count will be performed. The patient's past medical history, concomitant medications (including over the counter drugs and herbal supplements), and any recent symptoms (e.g., bleeding, shortness of breath, fatigue) will be reviewed to determine a potential etiology and make a clinical assessment of the significance of the finding. Refer to Appendix D for specific guidance.

9.2.2 Creatinine increase

If, at any visit, a creatinine increase of >0.3 mg/dL (27 μmol/L) from baseline is observed, a repeat chemistry will be performed. The patient's past medical history, concomitant medications (including over the counter drugs and herbal supplements), and any recent symptoms (e.g., fatigue, malaise, polyuria/oliguria, or palpitations) will be reviewed to determine a potential etiology and

make a clinical assessment of the significance of the finding. Refer to Appendix D for specific guidance.

9.2.3 Possible muscle and liver injury

For muscle injury, CK, hepatic, and renal function laboratory data will be integrated with myopathy signs and symptoms. For management of CK elevations > 3 ULN, refer to Appendix D.

For liver injury, laboratory data will be integrated with hepatic signs and symptoms. Monitoring and subsequent management of subject transaminase elevations is dependent upon baselinelevels, either < 2x ULN or ≥ 2x ULN at baseline. Refer to Appendix D for specific guidance and/or discontinuation of study drug recommendations.

9.2.4 Significantly elevated TG levels

In the event we see triglycerides>2000 mg/dL in a patient who did not have this high level at onset (many patients have very high triglycerides and no available therapy works for long term in the setting of the American diet and the social pressures, and this is one of the reasons why we want to undertake this study), we will contact the patient to review signs and symptoms of pancreatitis and we will evaluate diet information, have the patient meet with a dietician to manage adherence to a heart-healthy diet, counsel patients regarding restricted alcohol intake and diabetic control. We will repeat TG levels in 1 week. We will also measure lipase levels in the follow-up blood draw.

9.2.5 Patients with Diabetes

In patients with diabetes, we will adjust concomitant medications to prevent hypoglycemia. However, given the short nature of the study, we will not add any new medications to rescue for hyperglycemia unless fasting glucose levels exceed 230 mg/dL and/or patients have symptoms. Both hypoglycemia and hyperglycemia, as defined as fasting glucose >230 mg/dL will be captured as lipodystrophy events.

9.3 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;

NOTE: An adverse event or adverse reaction is considered “life-threatening” if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency or drug abuse.

9.4 Adverse Event Reporting − Procedures for Sponsor Investigator

9.4.1 Non-serious Adverse Events

Each AE will be reported to the study investigator and the study investigator is responsible for completing and signing off on the AE reports. Non-serious AEs will be reported to Gemphire in aggregate at the end of the study. The sponsor investigator will review a summary of all AEs monthly and document this review.

FPLD related events that are common in the study population (expected) and will be considered study endpoints include: cardiac events, worsening abdominal pain requiring emergency room visits, urinary tract infections, acute pancreatitis in a patient with recurrent episodes of pancreatitis, hypoglycemia or hyperglycemia, DKA or hyperosmolar state.

These and any other adverse events will be recorded on the CRF and monitored to resolution or 30 days after end of the study.

9.4.2 Serious Adverse Event Reporting

The sponsor investigator will report any qualifying Serious Adverse Event to MMS Holdings, Pharmacovigilance Department within 24 hours of learning of such event. In addition to MMS Holdings, the Sponsor-Investigator may, at her discretion, report the SAE to any other required regulatory agencies, including the University of Michigan IRBMED according to IRBMED policy.Any serious adverse event (SAE), whether or not considered study intervention related,

including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

Study endpoints that are serious adverse events (e.g., FLP expected events) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). All events must be reported to MMS Holdings Pharmacovigilance, on behalf of Gemphire, within 24 hours of learning of such event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the participant is stable.

The study sponsor (Dr. Elif Oral) with assistance from the MICHR MIAP group, will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than seven calendar days after the sponsor's initial receipt of the information. Unexpected, suspected serious adverse events will be reported to the FDA within 15 calendar days after the sponsor's initial receipt of the information. In addition, Gemphire must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

All observed or volunteered SAEs regardless of treatment group or suspected causal relationship to the study drug will be reported as described below. If a SAE occurs, reporting to MMS Holdings Pharmacovigilance (Gemphire and Sponsor-Investigator's Designee) must occur within 24 hours of learning of the event. Reporting to UM IRBMED will be done according to IRBMED reporting guidelines.

All SAEs and follow-up information must be reported to Gemphire or designee within two weeks of awareness of the event as required by your local requirements by emailing or faxing a completed SAE report form to the following:

Safety Contact Information: MMS Drug Safety

Facsimile: +734 468 6352

E-mail: GemphireDrugSafety@mmsholdings.com

In particular, if the SAE if fatal or life-threatening, notification to Gemphire or designee must be made within one week, irrespective of the extent of available AE information.

This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports, initial and follow-up reporting of exposure in utero (EIU) cases, and any SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period.

The Investigator must continue to follow the subject as medically necessary until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

9.5 Pregnancy Reporting

If a patient participating in the study becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should complete the Exposure *In Utero* form and report the pregnancy within 24 hours to:

Safety Contact Information: MMS Drug Safety

Facsimile: +734 468 6352

E-mail: GemphireDrugSafety@mmsholdings.com

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The patient should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify MMS Drug Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

9.6 Expedited Reporting

The Sponsor Investigator will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening to the Food and Drug Administration (FDA) in accordance with 21 CFR 312.32 Information will also be submitted to the University of Michigan IRB (IRBMED) in accordance with IRBMED reporting guidelines.

All other suspected unexpected serious adverse reactions will be reported to the FDA in accordance with 21 CFR 312.32 and the IRBMED in accordance with IRBMED reporting guidelines.

A copy will be sent to Gemphire as agreed upon in the Clinical Trial Agreement.

9.7 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be collected at the visits shown in the Schedule of Procedures (Appendix A) and the data captured will be forwarded to the site's local laboratory for evaluation. Assessments that require a patient to fast will be defined as no food or caloric beverage for at least eight hours prior to sample collection. Patients will be permitted to have water.

Local laboratory results that appear potentially misleading based on the Investigator's clinical assessment and review of the patient's medical history may be repeated for confirmation of the finding. Reassessments of non-qualifying screening labs must be reviewed and approved by the Principal Investigator prior to obtaining the new specimen. The clinical rationale for performing repeat testing of screening assessments should be thoroughly documented.

9.8 Vital Signs

Measurement of vital signs will include an assessment of pulse rate, blood pressure, respiration rate, and temperature. Vital signs will be measured according to the Schedule of Procedures (Appendix A). Blood pressure should be obtained in the seated position, after the patient has rested comfortably for at least five minutes. Blood pressure at the Screening Visit should be obtained in both arms and the arm with the highest value should be used for ongoing monitoring throughout the rest of the study. If an automated assessment is performed, the same machine should be used for the patient throughout the study when possible. Care should be taken to ensure an appropriate cuff size is utilized.

9.9 Electrocardiograms

Electrocardiograms will be performed in triplicate and sent to a central reviewer. Patients should be lying quietly in a fully supine position for at least 10 minutes prior to each 12-lead ECG. A 12-lead ECG will be performed according to the Schedule of Procedures (Appendix A).

The Investigator will assess ECG data as normal, abnormal not clinically significant, or abnormal clinically significant. Any clinically significant abnormalities should be documented as medical history, adverse event, or SAE, as applicable. All ECG traces will be kept as source data.

9.10 Physical Examinations

A full physical examination will be performed according to the Schedule of Procedures (Appendix A). A full physical examination includes genitourinary examination per the Investigator's discretion and does not include a rectal examination.

A symptom-directed physical examination will be conducted at other visits. See Schedule of Procedures (Appendix A).

Height and weight will be measured according to the Schedule of Procedures (Appendix A).

9.11 Medical/Surgical History and Demographics

Medical and surgical history and demographics will be recorded according to the Schedule of Procedures (Appendix A). Patient eligibility will be evaluated to determine all inclusion and none of the exclusion criteria are met. The Investigator will inquire with the patient at Study Day 1 to determine if there have been any changes in the patient's health affecting eligibility or requiring an update to their medical and surgical history.

9.12 Reserve Samples

Additional blood samples will be collected according to the Schedule of Procedures (Appendix A) to be available for analysis of exploratory biomarkers associated with lipid metabolism and FPLD and/or repeat or additional clinical laboratory and urine testing in the event of a safety issue.

9.13 Dual Energy X-Ray Absorption Scan (DEXA)

DEXA (Dual X-ray absorptiometry) scan for total body composition: This involves using a dual X-ray absorptiometer (Hologic Inc., Bedford, MA) for estimation of fat and lean body mass. Its

validity has been shown in multiple studies with various groups of patients. A DEXA scan will be performed according to the Schedule of Procedures (Appendix A).

10 STATISTICS

10.1 Sample Size

The sample size of eight patients (four per group) was empirically determined to provide expanded use proof of concept and initial safety and tolerance in the FPLD population.

10.2 Analysis Populations

10.2.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized patients who received at least one dose of study drug, and have both a baseline and at least one post-baseline lipid value. All efficacy summaries and analyses will be performed using the FAS.

10.2.2 Safety Analysis Set

The safety analysis set (SAS) will include all randomized patients who receive at least one dose of study drug. All safety analyses will be conducted on SAS.

10.3 Statistical Methods

10.3.1 Analysis of Efficacy

10.3.1.1 Primary efficacy analyses

The primary efficacy endpoint is the percent change from baseline to Week 12 in fasting serum TG. If the Week 12 TG value is missing, then the "Week 12" TG value will be imputed using last observation carried forward (LOCF).

Baseline will be defined as the average of the pre-dose Day 1/Visit T1 value and the last qualifying screening visit.

The primary efficacy endpoint will be summarized by treatment group and timepoint using the FAS.

10.3.1.2 Secondary efficacy analyses

Secondary efficacy endpoints will also be summarized by treatment group and timepoint, using the FAS.

The secondary TG efficacy endpoints are the change from baseline to Week 12 and change and percent change from baseline to the average of Weeks 6 and 12, and Week 24 in fasting serum TG. Baseline will be defined as outlined above for the primary variable. For the "average of Weeks 6 and 12" TG efficacy assessment, if only the Week 6 or Week 12 TG value is available, then that single value will be used. If both the Week 6 and Week 12 TG values are missing, then the average "Week 6 and Week 12" TG value will be imputed using LOCF. For the "Week 24" TG efficacy assessment, if Week 24 values are missing, then the value will be imputed using LOCF.

The change and percent change in all other secondary efficacy biomarkers will be summarized for Week 12 and Week 24 as described above.

Baseline TC, HDL-C, and LDL-C are defined similarly to baseline for TG. Baseline for fasting lipoproteins, hsCRP, SAA, IL-6, fibrinogen, IL-1β, ANGPTL4, ANGPTL3, are defined as the value from pre-dose Day 1/Visit T1.

An additional secondary analysis is change and percent change from baseline to Week 12 and Week 24 in the percentage of hepatic steatosis (liver fat content) as measured by MRI-PDFF. Baseline liver fat content is defined as the value from Screening. Missing percentage liver fat content at Week 24 will be imputed using last LOCF.

Hepatic fibrosis as measured by MR elastography will be summarized as outlined above for liver fat content via MRI-PDFF.

An additional secondary analysis in change and percent change from baseline to Week 24 in NAS as determined by histology.

10.3.1.3 Exploratory analysis

The exploratory variables will be summarized as described above. Missing values will be imputed using LOCF.

10.3.1.4 Missing Data

The primary analyses of the primary, secondary and exploratory (if measured and analyzed) outcome variables will use LOCF for missing value.

In the case of the presence of a substantial amount of missing data, sensitivity analyses will be carried out to evaluate the possible impact of missing data and may include multiple imputation or other techniques that allow for missing not at random.

To summarize laboratory variables, consecutive time windows will be created around each planned visit. In the descriptive statistics of laboratory variables, only measurements from scheduled visits will be used if values are available. If no values from a scheduled visit are available but values from unscheduled visits are available, the values from the last unscheduled visit from that window will be used for the summary statistics. The results of all laboratory values from unscheduled and repeat measurements will be recorded in the clinical database. In listings and narratives, all laboratory values including unscheduled and repeat values will be included.

10.3.2 Analysis of Safety

Safety will be assessed using the SAS. The assessment of safety will include adverse events, clinical laboratory assessments, ECGs, physical examinations, and vital signs. The safety analysis will be based primarily on the frequency of new or worsening adverse events, laboratory abnormalities, and SAEs. Other safety data will be summarized as appropriate.

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group, system organ class, and preferred term.

Safety laboratory data will be summarized by treatment group at baseline, End of Treatment (Week 24), or the ET Visit, if applicable, and change from baseline to End of Treatment (Week 24) or the ET Visit, if applicable. Frequency counts of new or worsening abnormalities will also be provided.

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

Data will be recorded directly into the Medrio EDC system. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An CRF will be considered complete when all missing, incorrect, and/or inconsistent data are provided. Study data monitoring will be performed by Gemphire Therapeutics or its designee.

11.1.1.1 Computer Systems

Data will be collected and processed using Medrio, a 21 CFR Part-11-compliant data capture system provided by Gemphire Therapeutics.

11.1.1.2 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. All passwords will be strictly confidential.

11.1.1.3 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA for medical history and adverse events, and
- World Health Organization Drug (WHO Drug) Dictionary for prior and concomitant medications.

11.1.2 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to sponsor investigator for resolution through data queries.

The paper CRFs must be reviewed and signed by the Investigator.

11.2 Record Keeping

Records of patients, source documents, monitoring visit logs, CRFs, inventory of study product, regulatory documents, and other correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Trial Agreement. Prior to transfer or destruction of these records, the Drug Manufacturer must be notified in writing and be given the opportunity to further store such records.

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

12.2 Institutional Review Board/Ethics Committee

Federal regulations and the International Conference on Harmonisation (ICH) require that approval be obtained from an Institutional Review Board (IRB)/Ethics Committee (EC) prior to participation of patients in research studies. The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/EC approval has been obtained. The protocol, Investigator's Brochure, Informed Consent Form (ICF), advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/EC by the Investigator.

Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study being provided to a patient or patient's legal guardian must be approved by the IRB/EC.

No drug will be released to the site for dosing until written IRB/EC authorization has been received by the Sponsor, or designee.

12.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/EC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator, or a person delegated the responsibility by the Investigator, must ensure that each study patient (or legally acceptable representative) is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator or delegate will allow the patient adequate opportunity to read the written informed consent and ask any questions. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to any study-specific activity. The original signed copy of the ICF must be maintained by the Investigator and is patient to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/EC and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

12.4 Study Monitoring

To assure adequate protection of the rights of human subjects, per 21 CFR §312.50, 312.53, this study will be monitored by Gemphire Therapeutics or its designee in addition to the University of Michigan Institute for Clinical and Health Research (MICHR) (if needed). Routine monitoring will be scheduled at appropriate intervals, with more frequent visits occurring at the beginning of the study. An initiation visit will take place, followed by routine monitoring visits.

Monitoring visits may be in the form of a site visit or a review of documents. During a monitoring visits, access to relevant hospital and clinical records must be given by the investigator to the Gemphire and the MICHR representative (if required) conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. It is expected that the relevant investigational staff be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during the site visits will be communicated with the investigator and an expected to be resolved in timely fashion.

The established monitoring plan will ensure the quality and integrity of the data through pre-investigation visits and periodic site visits to verify adherence to the protocol, completeness and accuracy of study data and samples collected, proper storage, dispensing and inventory of study medication, and compliance with regulations.

12.5 Data Safety Monitoring Board

A Data Safety Monitoring Board will convene every quarter during study patient activity to review safety data for this study. This board will consist of two physicians and a statistician. De-identified patient data will be provided with case numbers. In addition, the DSMB will review all the SAEs. If there is a reason to stop therapy in a particular patient, the DSMB will direct the Principle Investigator. Also, the DSMB may decide to halt this study if there is a pattern of SAEs.

12.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, other regulatory bodies, and the IRB/EC as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

12.7 Retention of Records

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. It is

the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed ICFs, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from Gemphire before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, University of Michigan and Gemphire should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

12.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Sponsor Investigator is obligated to keep data pertaining to the study confidential. Gemphire and Investigator reserve the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

12.9 Financial Disclosure

Clinical Investigators are required to provide financial disclosure information to fulfill Sponsor obligations under 21 CFR §54. In addition, this information will be promptly updated if any relevant changes occur during the study and for a period of one year after the completion of the study.

12.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Gemphire has taken out clinical trial insurance. This insurance provides coverage to the sites through Gemphire in the event of physical injury or death related to the study drug or any procedure related to the protocol.

12.11 Legal Aspects

The clinical study will be submitted as an Investigator Initiated IND.

The study will commence (i.e., initiation of study site) when the FDA authorization and favorable Ethics opinion have been received.

12.12 Definition of End of Study

The End of Study for each patient is defined as the completion of the Follow-up Visit or the ET Visit, if applicable.

12.13 Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of University of Michigan. In addition, Gemphire retains the right to discontinue development of gemcabene at any time.

If the development of gemcabene is prematurely terminated or discontinued, Gemphire will promptly notify the Investigator. After notification, the Investigator must contact all participating patients within two weeks.

13 STUDY ADMINISTRATIVE INFORMATION

13.1 Protocol Amendments

All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented only after it is approved by the IRB and submitted to the FDA, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within five working days.

13.2 Address List

13.2.1 Sponsor

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University of Michigan
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13.2.2 Drug Supplied By:

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13.2.3 Biological Specimens

University of Michigan Clinical Pathology Laboratories
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APPENDIX A: SCHEDULE OF PROCEDURES

	Pre-Screen[a]	Screening Period		Up to Day -3 to Day 1	Treatment Period[b]						Follow-Up[c]	ET
		Study Day -28			Week 4	Week 8	Week 12	Week 16	Week 20	Week 24[c]	Week 28	
		Visit S1	Visit S2	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5	Visit T6	Visit T7	FU8	
Informed consent[a]	X	X										
Inclusion/exclusion criteria[a]	X	X	X									
Medical/surgical history and demographics[a]	X	X	X									
Full physical examination[d]	X	X								X		X
Symptom-directed physical examination				X	X		X			X	X[e]	
Initiate wash-out	X											
Vital signs[f], height[g], and weight, BMI	X	X	X	X	X		X			X		X
Urinalysis; Protein:creatinine; albumin:creatinine[h]	X	X		X	X	X	X	X	X	X	X[e]	X
Serum/urine pregnancy test[i]	X	X		X	X		X			X[i]	X[e]	X
Safety chemistry panel, coagulation, and hematology[j]	X	X	X	X	X	X	X	X	X	X[i]	X[e]	X
TSH and serology	X											
Fasting lipid panel[l] LDL-C ultracentrifugation	X[r]	X[s]	X	X	X	X	X	X	X	X	X	X
Fasting apolipoproteins[m]				X			X			X	X	X
hsCRP, SAA, IL-6 and fibrinogen				X			X			X	X	X
Fasting insulin, FPG, HbA1c	X	X		X			X			X		X
MRI-PDFF; MR elastography	X						X			X		X
Liver Biopsy[n]				X						X		
QOL questionnaires		X		X			X			X		X
Randomization							X					
Study drug administration				X	X		X					
Compliance check					X	X	X	X	X	X	X	X
Dietary assessment (self-reported)[o]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[p]		X		X	X		X			X		X

Adverse events	X[q]	X[q]	X[q]	X	X	X	X	X	X	X	X	X
Dual Energy X-ray Absorption Scan	X						X			X		
Concomitant medications	X	X	X	X	X		X			X	X	X
Reserve samples for exploratory measures				X			X			X	X	X
Reserve genotyping sample				X								

a. All eligible patients will participate in the Screening Visit up to 28 days prior to Day 1. Only patients with a history within the past year of TG ≥ 200 mg/dL on current TG-lowering therapy and requiring a Wash-Out Period will participate in the Pre-Screening Visit.
b. Study assessments will be completed ±3 days for study visits with the exception of study visit T4 (Week 24) when assessments can be performed up to 3 days prior to Week 24, but not after Week 24.
c. The Follow-up Visit will be conducted as a telephone call 4 weeks (±3 days) after the last dose of study drug, unless the patient requires a site visit due to an abnormal result at Week 24 or an ongoing treatment-related adverse event.
d. A full physical examination includes genitourinary examination per the Investigator's discretion and does not include a rectal examination.
e. Only for patients who had an abnormal result at Week 24 or an ongoing treatment-related adverse event.
f. Vital signs include pulse rate, blood pressure, respiration rate, and temperature. Blood pressure should be obtained in the seated position, after the patient has rested comfortably for at least 5 minutes. Blood pressure at the Screening Visit should be obtained in both arms and the arm with the highest value should be used for ongoing monitoring throughout the rest of the study. The same machine should be used for the patient throughout the study.
g. Height will be measured only at the Screening Visit.
h. A urine microscopic examination will be performed when the dipstick result is abnormal (positive for blood, leukocyte esterase, or nitrites). Urine protein:creatinine ratio will be performed at the Screening Visit, Day 1, Week 6, Week 12 and Week 24, the Follow-up Visit (only for patients who had an abnormal result Week 24 [or the ET Visit, if applicable) or an ongoing treatment-related adverse event]), and the ET Visit, if applicable.
i. For women of child-bearing potential only, a serum pregnancy test will be conducted at the Screening Visit, and the ET Visit, if applicable. A urine pregnancy test will be conducted at Day 1, Week 6, Week 12 and Week 24.
j. See Appendix B for a list of analytes and description of when repeat or reflexive testing will be required.
k. Thyroid-stimulating hormone and serology will be measured at the Screening Visit. Serology includes HBV, HCV, and HIV. HbA1c will be collected at Screening Visit, Week 12, and Week 24.
l. Includes TG, non-HDL-C, TC, HDL-C, and VLDL-C. Fasting will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Patients will be permitted to have water.
m. Includes total ApoB, ApoA-I, ApoA-II, ApoC-II, ApoC-III, ApoE, and Lp(a). Fasting will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Patients will be permitted to have water.
n. Liver biopsy will be optional for subjects.
o. Patients will self-report their adherence to a stable diet.
p. Patients should be lying quietly in a fully supine position for at least 10 minutes prior to each 12-lead ECG.
q. Serious Adverse Events that occur prior to the first dose of study drug (Day 1) should be reported as an update to medical history as well as be reported on the appropriate adverse event CRF.
r. LDL-C ultracentrification will not be performed at the Pre-Screening Visit.
s. An addition fasting TG may be assessed at an "optional" visit between S1 and S2.

Apo = apolipoprotein; ECG = electrocardiogram; ET = Early Termination; HBV = hepatitis B virus; HbA1c = hemoglobin A1c; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; non-high-density lipoprotein cholesterol = non-HDL-C; TC = total cholesterol; TG = triglyceride; TSH = thyroid-stimulating hormone; VLDL-C = very low-density lipoprotein cholesterol.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

- Alanine aminotransferase
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase
- Bicarbonate
- Blood urea nitrogen
- Calcium
- Chloride
- Creatine kinase
- Creatinine [1]
- Gamma-glutamyl transferase
- Glucose
- Lactate dehydrogenase
- Phosphorus
- Potassium
- Sodium
- Total bilirubin [2]
- Total protein
- Estimated glomerular filtration rate (GFR) [3]

1. For a creatinine increase of >0.3 mg/dL (27 µmol/L) from baseline during the study, repeat chemistry will be performed.
2. If total bilirubin is elevated, reflexive direct bilirubin testing will be performed.

Endocrinology

- Thyroid-stimulating hormone

Hematology

- Hematocrit
- Hemoglobin [1]
- Platelet count
- Red blood cell count
- Mean corpuscular hemoglobin concentration
- Mean corpuscular hemoglobin
- White blood cell count and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) [2]
- Mean corpuscular volume

1. For a hemoglobin decrease of >1.5 g/dL from baseline during the study, repeat hematology studies and reflexive evaluation of reticulocyte count will be performed.
2. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis [1]

pH	Proteinuria [2]
Ketones	Blood
Leukocyte esterase	Specific Gravity
Glucose	Bilirubin
Nitrite	
Albumin	

1. A urine microscopic examination will be performed when dipstick results are abnormal (positive for blood, leukocyte esterase, or nitrites).
2. Urine protein:creatinine ratio will be performed at the Study Day 1 and Week 12, the Follow-up Visit (only for patients who had an abnormal result at Week 12 or an ongoing treatment-related adverse event), and the ET Visit, if applicable.

Pregnancy Test

Serum and urine pregnancy tests will be administered to all female patients of child-bearing potential.

Serology

Hepatitis B	Hepatitis C
Human Immunodeficiency Virus	

Coagulation

Prothrombin time	Activated partial thromboplastin time
International normalized ratio	

Efficacy Parameters

The following efficacy parameters will be assessed in this study:

Apo A-I	ApoA-II
ApoB	ApoC-II
ApoA-V	ApoC-III
Triglycerides	ApoE
High-density lipoprotein cholesterol	Low-density lipoprotein cholesterol
Non-high-density lipoprotein cholesterol	Very low-density lipoprotein cholesterol
SAA	Total cholesterol
High-sensitivity C-reactive protein	IL-6
HbA1c	Fibrinogen
Adiponectin	FPG
Leptin	Insulin
HbA1c	ANGPTL3
	IL-1β
	ANGPTL4

APPENDIX C: NEW YORK HEART ASSOCIATION CONGESTIVE HEART FAILURE CLASSIFICATION

- Class I: patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II: patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III: patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV: patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: The Criteria of the New York Heart Association. Nomenclature and Criteria for Diagnosis of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

APPENDIX D: HEMATOLOGY, RENAL, MUSCLE INJURY AND HEPATIC MONITORING

Hematology

For a hemoglobin decrease of > 1.5 g/dL from baseline during the study, repeat hematology studies and reflexive evaluation of reticulocyte count will be performed. The patient's past medical history, concomitant medications (including over the counter drugs and herbal supplements), and any recent symptoms (e.g., bleeding, shortness of breath, fatigue) will be reviewed to determine a potential etiology and make a clinical assessment of the significance of the finding. If hemoglobin falls >3.0 g/dL without any clear cause, then the investigator should discontinue the investigational product and hemoglobin should be monitored until it returns to a level of no less than 1.0 g/dL below baseline. At this time the investigator can consider restarting the investigational product and recheck hemoglobin levels 1 and 2 weeks after re-initiation of investigational product. If hemoglobin levels decrease >3 g/dL again, investigational product should be discontinued and the subject should continue with all other study procedures.

Hemoglobin should continue to be monitored until it returns to a level of no less than 1.0 g/dL below baseline.

Renal

Renal function and potential nephrotoxicity will be assessed via hematology and urinalysis throughout the study. If, at any visit, a creatinine increase of > 0.3 mg/dL (27 μmol/L) from baseline or a > 30 urinary albumin:creatinine ratio mg/g is observed, a repeat chemistry/urinalysis will be performed within 1 week. The patient's past medical history, concomitant medications (including over the counter drugs and herbal supplements), and any recent symptoms (e.g., fatigue, malaise, polyuria/oliguria, or palpitations) will be reviewed to determine a potential etiology and make a clinical assessment of the significance of the finding.

Patients with persistent serum creatinine changes of > 0.3 to < 0.5 mg/dL will be evaluated by the investigator to determine if the subject has any signs and symptoms of renal injury. If the investigator determines that the biomarkers along with the signs and symptoms are consistent with renal injury then investigational product should be discontinued and the subject should continue with all future protocol assessments.

If, at any visit, there is a creatinine increase ≥0.5 mg/dL from baseline and > ULN, a repeat chemistry will be performed within one week. The subject's pase medical history, concomitant medications (including over the counter drugs and herbal supplements0, and any recent symptoms (e.g. fatigue, malaise, polyuria/oliguria, or palpitations) will be reviewed to determine a potential etiology and make a clinical assessment of the significance of the finding. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to baseline or normal levels.

If at any time there is a doubling of serum creatinine or a decrease >50% in GFR from baseline, then investigational product should be discontinued immediately. The patient will be followed until renal parameters return to baseline or normal levels. The investigator can determine based on signs, symptoms and laboratory data whether or not to reinitiate investigational product and continue with scheduled monitoring. Regardless of whether or not investigational product is reinitiated subjects should continue with all future protocol assessments.

Muscle Injury

Muscle injury will be assessed using a combination of clinical signs and symptoms and laboratory data (creatine kinase [CK], hepatic, and renal function).

All patients with suspected or confirmed muscle injury should be managed according to the standard of care at the discretion of the Investigator.

- Patients with new or unexplained muscle symptoms should have an unscheduled visit scheduled within 7 days of site notification. At this visit, samples should be sent for a full chemistry panel, including CK, liver, and renal function.
- Patients with CK elevations of >3 × upper limit of normal (ULN) who are asymptomatic should be considered for an unscheduled visit (+ isozymes), based upon medical judgment.
- All patients with CK elevations >10 × ULN should have an unscheduled visit (+ isozymes) within 1 week. Study drug should be temporarily discontinued, pending the results of an investigation into the cause of muscle injury and/or CK elevation returns to within normal range or to a level deemed acceptable by the Investigator, or until the abnormality is explained by an appropriate diagnosis. Any statin the patient is currently taking will be temporarily discontinued while the cause of the muscle injury is being investigated. The investigator can determine if it is appropriate to reinitiate study drug. If study drug is reinitiated, then CK assessments should be made with 7 days to ensure that recurrence is not seen. If there is recurrent elevations >5 x ULN after reinitiating study drug, then study drug should be permanently discontinued and the patient's CK and renal function followed until they return within normal range or to a level deemed acceptable by the Investigator, or until the abnormality is explained by an appropriate diagnosis. If study drug is permanently discontinued the subject should continue with all future protocol assessments.

It is important that patients are instructed to not undertake any form of strenuous physical activity for at least 24 hours prior to repeat blood testing.

Hepatic Monitoring: Subjects with baseline transaminases < 2x ULN

Subjects with hepatic enzyme elevations should be managed according to the standard of care, at the discretion of the Investigator. For subjects with signs or symptoms suggestive of hepatitis, an unscheduled visit and a chemistry panel should be performed. Subjects with an ALT or AST > 3 × ULN should have an unscheduled visit. A repeat assessment should be performed as soon as possible (within 1 week) to confirm the finding. A clinical evaluation should be performed,

including assessment of past medical history (including non-alcoholic fatty liver disease/steatohepatitis and alcohol use) and concomitant medications (including over the counter drugs and herbal supplements). Risk factors for hepatitis infection should be reviewed and hepatitis studies should be performed. Non-study drug potential causes for transaminase elevations should be ruled out. The investigator may consider to temporarily suspend study drug and reassess liver function weekly until they return within normal range or to a level deemed acceptable by the Investigator, or until the abnormality is explained by an appropriate diagnosis.
The possible dosing re-initiation (re-challenge) or follow-up schedule for any events meeting these criteria will be determined by the Investigator in consultation with the Medical Monitor.

Recommended Hepatic Discontinuation Criteria: Baseline Transaminase < 2x ULN

Study drug should be discontinued permanently if any one of the following occurs (as confirmed by repeat assessment) and if the event is without an alternative explanation:

- ALT or aspartate aminotransferase (AST) > 8 × ULN;
- ALT or AST > 5 × ULN for more than 2 weeks;
- ALT or AST > 3 × ULN and either total bilirubin > 2 × ULN or international normalized ratio > 1.5; and/or
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

It is also recommended that statin regimen is discontinued if any of the above criteria is met. Abnormal values should be followed until they return within normal range or baseline range or to a level deemed acceptable by the Investigator, or until the abnormality is explained by an appropriate diagnosis. If study drug is permanently discontinued the subject should continue with all future protocol assessments.

Hepatic Monitoring: Subjects with baseline transaminases ≥ 2x ULN

If subjects with abnormal baseline liver indices develop elevations of AST or ALT >2x baseline or total bilirubin >1.5x baseline values during the study, repeat testing should be performed within 48 -72 hours. If there are persistent elevations (ALT or AST >2x baseline or TBL >1.5x baseline values) upon repeat testing, then close observation (testing and physical examination 2-3 times per week) should be implemented and discontinuation of drug should be considered. Recommended Hepatic Discontinuation Criteria: Baseline Transaminase ≥ 2x ULN Study drug should be discontinued permanently if any one of the following occurs (as confirmed by repeat assessment) and if the event is without an alternative explanation:

- If BLM ≥2x ULN but <5x ULN, discontinue if ALT or AST increases to >3x BLM
- Discontinue if ALT or AST increase is >2x BLM AND the increase is accompanied by a concomitant increase in TBL to >2x BLM OR the INR concomitantly increases by >0.2
- In any subjects with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).