Title: A 12-Week, Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy Safety and Tolerability of Gemcabene in Subjects with Severe Hypertriglyceridemia (INDIGO-1)

NCT ID: NCT02944383

Approval Date: 17-Mar-2017

CLINICAL STUDY PROTOCOL

A 12-Week, Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy Safety and Tolerability of Gemcabene in Subjects with Severe Hypertriglyceridemia (INDIGO-1)

Investigational Product: Gemcabene calcium tablets (gemcabene)
Protocol Number: GEM-401

Sponsor:
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Version Number: 1.0; September 26, 2016
Amendment #1; Version Number: 2.0; November 11, 2016
Amendment #2; Version Number: 3.0; December 22, 2016
Amendment #3; Version Number: 4.0; March 17, 2017

SIGNATURE PAGE

STUDY TITLE: A 12-Week, Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety and Tolerability of Gemcabene in Subjects with Severe Hypertriglyceridemia (INDIGO-1)

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

Signature Date

PI

3/16/2017

Gemphire Therapeutics Inc.

PI

3/16/2017

We, the undersigned, have reviewed this protocol.

Signature Date

PI

3/17/2017

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol in its entirety. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Gemphire Therapeutics Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Gemphire Therapeutics Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Gemphire Therapeutics Inc. with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Conference on Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Printed Name

SYNOPSIS

TITLE: A 12-week, Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety and Tolerability of Gemcabene in Subjects with Severe Hypertriglyceridemia (INDIGO-1)

PROTOCOL NUMBER: GEM-401

INVESTIGATIONAL PRODUCT: Gemcabene calcium oral tablets (gemcabene)

PHASE: 2

INDICATION(S): Treatment with gemcabene is indicated as an adjunct to diet to reduce serum triglyceride (TG) levels in adult patients with severe hypertriglyceridemia (≥500 mg/dL); where lowering TG levels below 500 mg/dL may decrease a patient's risk for developing pancreatitis.

OBJECTIVES:

The primary objective of this study is to assess the effect of gemcabene 300 mg and 600 mg once daily (QD) compared to placebo on fasting serum TG levels after 12 weeks of treatment in subjects with severe hypertriglyceridemia (≥ 500 mg/dL to < 1500 mg/dL) on a self-reported, stable, heart-healthy diet.

The secondary objectives of this study are the following:

- To assess the safety and tolerability of gemcabene 300 mg and 600 mg QD in subjects with severe hypertriglyceridemia;
- To assess the effect of gemcabene 300 mg and 600 mg QD oral tablets on other lipid and apolipoprotein parameters, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), serum amyloid A (SAA), angiopoietin like 4 (ANGPTL4), adiponectin, and fibrinogen after 12 weeks of treatment.

The exploratory objectives of this study are the following:

- CI [redacted]

POPULATION:

The population for this study includes adult male and female subjects ≥18 years of age. Subjects must have an (average) fasting TG value ≥ 500 mg/dL to < 1500 mg/dL during the Screening

Period, while on a self-reported stable, heart-healthy diet.

STUDY DESIGN:

Pre-Screening (Wash-Out Period): A Wash-Out Period will be required for potential subjects taking any lipid-regulating therapies or supplements, with the exception of statins or ezetimibe 10 mg QD. For subjects requiring a Wash-Out Period, the Pre-Screening Visit will be their first study visit and will occur anywhere from 4 to 8 weeks prior to the Screening Visit (S1, Week -4) based on the type of lipid-regulating therapy and its associated duration of wash-out required.

Subjects currently taking lipid-altering medications such as: niacin > 200 mg/day, fibrates, prescription or over-the-counter fish oil or other products containing omega-3 fatty acids (OMG-3), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, bile acid sequestrants, or other herbal products or dietary supplements with potential lipid-altering effects, must be able to safely discontinue therapy at the Pre-Screening Visit. The duration of the Wash-Out Period will be dependent upon the status of the subject's current lipid-regulating therapy. Specifically, PCSK9 inhibitors will require an 8-week Wash-Out Period, fibrates will require a 6-week Wash-Out Period, and niacin, OMG-3 compounds, bile acid sequestrants or other lipid-regulating therapies will require a 4-week Wash-Out Period prior to the Screening Visit. If the subject needs to be washed off more than one lipid-altering medication; the medication that requires the longest Wash-Out Period will be the default. For example, if a subject is taking OMG-3 and fibrates, then the subject would undergo a six-week Was-Out Period. Exception: if a potential subject is statin-naïve, or dosing only on a statin or ezetimibe (for at least 12 weeks) and not currently dosing on other lipid-altering medications, there is no requirement for a Pre-Screening Visit.

The Wash-Out Period will only be initiated after inclusionary lab values are received and reviewed. During this Wash-Out Period, potential subjects will be counseled on the importance of maintaining a heart-healthy diet and limiting alcohol intake.

Screening Period: This is the TG qualifying period. All potential subjects will participate in the Screening Period, including Screening Visit 1 (S1), Screening Visit 2 (S2) and, if necessary as outlined below, optional Screening Visit 3 (S3) up to 28 days prior to Study Day 1 (Visit T1). For potential subjects on stable statin and/or ezetimibe therapy for ≥ 12 weeks and who do not require a Wash-Out Period, S1 will be their first study visit. For other subjects who have been washing out their other lipid medications, S1 occurs after the full required washout has been completed.

During this Screening Period, potential subjects must meet the TG qualifying values to be eligible for randomization on Day 1 (Visit T1).

The screening visits can be completed up to 28 days but not less than 14 days prior to T1 (Day 1). The visits are provided with recommended timepoints; however the minimum time between visits can be as short as 1 week with the Screening Period as short as 14 days for qualification with S1 and S2 visits or 21 days for qualification with S2 and S3. At the end of this 2-4-week diet and lifestyle stabilization and TG qualifying period, eligible subjects must have an average fasting TG level ≥ 500 mg/dL to < 1500 mg/dL to qualify for randomization into the 12-week double-blind treatment period. The TG level for qualification will be based on the average

(arithmetic mean) of the Visit S1 and Visit S2 values. If a subject's average TG level from Visit S1 and Visit S2 falls outside the required range for entry into the study, one additional sample for fasting TG value can be collected 1 week later (at the Optional Visit S3), and the arithmetic mean from Visits S2 and S3 will then be used to determine eligibility.

Double-Blind Treatment Period: After confirmation of qualifying fasting TG values and all other inclusion and exclusion criteria, eligible subjects will be randomized and enter a 12-week, double-blind treatment period. At Visit T1, 90 eligible subjects will be randomized via an interactive web/voice response system (IWRS/IVRS) on Study Day 1 in a 1:1:1 ratio (30 subjects per group) to one of the following treatment groups:

- Gemcabene 300 mg QD, or
- Gemcabene 600 mg QD, or
- Placebo

Subjects will be stratified by baseline statin therapy (yes or no) and qualifying TG value (< 880 mg/dL or ≥ 880 mg/dL) to ensure background therapies and baseline TG values are balanced across all treatment groups.

The primary evaluation of efficacy will be at End of Study (EOS) (using the average of Week 10 [T4] and Week 12 [T5]). The Follow-up Visit (telephone call) will occur 4 weeks (± 3 days) after the last dose of study drug.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Study drug will be double-blinded and prepared in bottles with 30 days of dosing contained within each bottle. The subjects will be asked to take one tablet from each of the 2 bottles for a total of 2 tablets per day as outlined below:

- 300 mg: 30 gemcabene tablets in one bottle + 30 matching placebo tablet in a second bottle
- 600 mg: 2 bottles each containing 30 300 mg gemcabene tablets
- Placebo: 2 bottles each containing 30 placebo tablets.

The first dose of study drug will be administered at the site on Study Day 1. On days with a scheduled office visit with blood sample collection, subject will remain fasted and should not take gemcabene until after the blood samples are collected at the site. On all other days, the subject will self-dose: taking study drug at the same time in the morning with a full glass (approximately 8 ounces) of water either with or without food.

STATISTICAL ANALYSIS:

Sample Size

Approximately 90 subjects (30 subjects per treatment group) will be randomized into 1 of 3 treatment groups: gemcabene 300 mg, gemcabene 600 mg or placebo.

A sample size of 30 randomized subjects in the gemcabene 300 mg group, 30 randomized subjects in the 600 mg group and 30 randomized subjects in the placebo group is expected to

provide 80% power to detect a difference of 35% in the percent change in TG from baseline to End of Study (EOS) between either of the gemcabene treatment groups and the placebo group. This calculation is based on a 2-sided t-test at the 5% level of significance ($\alpha = 0.05$), a common standard deviation of 43, and a drop-out rate of 15%.

Subject Populations

Full Analysis Set: The Full Analysis Set (FAS) will consist of all randomized subjects who receive at least 1 dose of study drug and have at least 1 post-baseline efficacy assessment. The FAS population will be the primary analysis population. All efficacy analyses will be performed on the FAS population.

Per Protocol Set: The Per Protocol Set (PPS) will include all FAS subjects who complete the 12-week Treatment Period without major protocol deviations. The PPS will be used to assess robustness of the analysis results. Protocol deviations will be reviewed and the PPS will be determined prior to database lock.

Safety Analysis Set: The Safety Analysis Set (SAS) will include all randomized subjects who receive at least 1 dose of study drug. All safety analyses will be conducted on SAS.

EFFICACY ENDPOINTS AND ANALYSIS:

Primary Efficacy

The primary efficacy endpoint is the percent change in fasting serum TG from baseline to EOS. Baseline will be defined as the average of the (Screening Visits [S1 and S2] or [S2 and S3] occurring up to 28 days prior to Study Day 1) and Study Day 1 [pre-dose]) values. EOS will be defined as the average of Week 10 and Week 12. If either the Week 10 or Week 12 value is missing, then the single value (Week 10 or Week 12) will be used. Completely missing values (both Week 10 and Week 12) will be imputed using last observation carried forward (LOCF), with the last on-treatment value carried forward as the EOS value.

The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA) with percent change from baseline to EOS in TG as the dependent variable; treatment and baseline statin (yes or no) as factors; and baseline fasting serum TG as a covariate. The ANCOVA will be performed using the FAS, with subjects included in their randomized treatment group regardless of the treatment they actually received. The least-squares mean (LSM) and standard error (SE) will be provided for each treatment group, along with the placebo-corrected LSM, its 95% confidence interval (CI), and associated p-value for both gemcabene groups. A 2-sided test with a significance level of 0.05 will be used for the comparison of the gemcabene 300 mg and 600 mg groups separately to the placebo group. If non-normality is detected, then either the data will be transformed so that it is normally distributed or a nonparametric test will be used.

A confirmatory analysis of the primary efficacy endpoint will be performed using the PPS.

Secondary Efficacy

Secondary efficacy endpoints include:

- Change and percent change from baseline to Weeks 2, 6, 10 and 12 in fasting serum TG, and

change from baseline to EOS in fasting serum TG;

- Change and percent change from baseline to Weeks 2, 6, 10, 12 and EOS in total cholesterol (TC), non-HDL-C, HDL-C, and VLDL-C;
- Change and percent change from baseline to Weeks 10, 12 and EOS in Apo B, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, and ApoE;
- Change and percent change from baseline to Weeks 10, 12 and EOS in LDL-C (ultracentrifugation), LDL-TG, VLDL-TG, HDL-TG;
- Change and percent change from baseline to Week 12 in lipoprotein size and particle number (NMR);
- Change and percent change from baseline to Week 12 in hsCRP, IL-6, SAA, ANGPTL4, adiponectin and fibrinogen; and
- Percent of subjects achieving a TG value < 500 mg/dL (5.65 mmol/L) at EOS.

For continuous secondary efficacy endpoints, the same ANCOVA model outlined above for the primary efficacy endpoint will be used, with the respective baseline included as the covariate. Baseline for TC, non-HDL-C, HDL-C, and VLDL-C will be defined as the average of the last two pre-dose values (generally will be the average of Visit S2 and pre-dose Study Day 1/Visit T1). Baseline for fasting apolipoproteins, LDL-C (ultracentrifugation), LDL-TG, VLDL-TG, HDL-TG, hsCRP, IL-6, SAA, adiponectin, fibrinogen, and ANGPTL4 is defined as the value from pre-dose Study Day 1/Visit T1. For the EOS time point, EOS will be defined as the average of Week 10 and Week 12. If either the Week 10 or Week 12 value is missing, then the single value (Week 10 or Week 12) will be used. Completely missing values (both Week 10 and Week 12) will be imputed using LOCF, with the last on-treatment value carried forward as the EOS value. For all other time points, missing values will be imputed using LOCF, with the last on-treatment value carried forward to that time point.

Each ANCOVA will be performed using the FAS, with subjects included in their randomized treatment group regardless of the treatment they actually received. The output from each ANCOVA will include the LSM and SE for each treatment group, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value for both gemcabene groups. For every continuous endpoint (each parameter, each time point), if non-normality is detected, then either the data will be transformed so that it is normally distributed or a nonparametric test will be used.

The percent of subjects achieving a TG value < 500 mg/dL (5.65 mmol/L) will be analyzed using a logistic regression with treatment, baseline statin use (yes or no) and baseline TG value as independent factors. The percent of subjects in each treatment group achieving a TG value < 500 mg/dL, and the odds ratios with 95% confidence intervals and p-values will be presented to compare gemcabene 300 mg and gemcabene 600 mg separately with the placebo group.

The secondary efficacy analyses will be repeated using the PPS.

Exploratory Efficacy

The exploratory efficacy endpoints include:

- CI [redacted]

For each continuous exploratory endpoint, an ANCOVA will be performed, with the relevant baseline as the covariate. In general, baseline and EOS will be defined as described above in the primary and secondary efficacy analysis sections. Baseline for fasting insulin levels, FPG and HbA1c is defined as the value from pre-dose Study Day 1/Visit T1. The FAS will be used for each analysis, with subjects included in their randomized treatment group regardless of the treatment they actually received. For the analysis of fasting insulin levels, FPG and HbA1c, the FAS that includes only subjects with diabetes at baseline will be used. Where appropriate, relevant subgroups will be used (e.g., within each TG stratum). For each endpoint, the LSM and SE for each treatment group will be provided, along with the placebo-adjusted LSM, 95% CI and p-value for both gemcabene groups.

The percent of diabetic subjects with > 5% decrease in dosage of anti-diabetes pharmacologic treatment from baseline to Week 12 will be analyzed using logistic regression with treatment, baseline statin use (yes or no) and baseline TG value as independent factors. The percent of diabetic subjects in each treatment group with > 5% decrease, and the odds ratios with 95% confidence intervals and p-values will be presented to compare gemcabene 300 mg and 600 mg separately with the placebo group.

The exploratory efficacy analyses will be repeated using the PPS.

SAFETY ENDPOINTS AND ANALYSIS:

Secondary endpoints related to safety include adverse events, safety laboratory parameters (chemistry including cystatin-C, hematology, coagulation values); urinalysis including urine protein:creatinine ratio, urine albumin:creatinine ratio and neutrophil gelatinase-associated lipocalin; vital signs, electrocardiogram (ECG) results; and physical examinations (PEs).

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

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). The summarization of AEs will include only treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

Safety laboratory data will be summarized by treatment group at baseline, and at each post-baseline time point, if applicable, and change from baseline to End of Treatment (Week 12) or the ET Visit, if applicable. Baseline for safety laboratory data will be defined as the last pre-dose value (pre-dose Study Day 1/Visit T1 or prior). Frequency counts of new or worsening abnormalities will also be provided.

Vital signs data (value and change from baseline, where appropriate) will be summarized by treatment group at baseline and at each post-baseline time point. Baseline for vital signs data will be defined as the last pre-dose value (pre-dose Study Day 1/Visit T1 or prior). Abnormalities in ECGs and in PEs will be summarized.

All safety data will be listed.

SITES: Approximately 40-50 sites in the United States and Canada.

SPONSOR:

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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
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
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

Abbreviation	Definition
IWRS/IVRS	Interactive web/voice response system
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
LPL	Lipoprotein lipase
LSM	Least squares mean
MedDRA	Medical Dictionary for Regulatory Affairs
Lp-PLA2	Lipoprotein-associated phospholipase A2
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
RLP-C	Remnant lipoprotein cholesterol
RLP-TG	Remnant lipoprotein triglycerides
RLP-ApoB	Remnant lipoprotein apolipoprotein B
SAA	Serum amyloid A
SAE	Serious adverse event
SE	Standard error
SHTG	Severe hypertriglyceridemia
SOP	Standard Operating Procedure
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 (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 apolipoprotein C-III (apoC-III) protein.[1] This in turn unmasks 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-carboxylase (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.

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 Dose Selection

We conducted (1) a prospective analysis in a gemcabene monotherapy study (1027-04) in subjects with mild-moderate hypertriglyceridemia (baseline TG ≥ 200 mg/dL); (2) a retrospective integrated analysis of Phase 2 dyslipidemic studies that included subjects with baseline TG ≥ 200 mg/dL administered gemcabene monotherapy (1027-04, 1027-14 [healthy, obese subjects], and 4141001 [monotherapy arm of a study in hyperlipidemia subjects +/-

atorvastatin]); and (3) a retrospective integrated analysis of Phase 2 dyslipidemic studies that included subjects with baseline TGs ≥ 200 mg/dL administered gemcabene in combination with statin therapy (1027-18 and 4141001 [atorvastatin combination arms]) to determine the doses of gemcabene with the greatest TG lowering and the most favorable effects on LDL-C to test further in Phase 2 to support Phase 3. Gemcabene 300 mg and the 600 mg were selected for following reasons:

- The 300 mg once daily (QD) dose is optimal based on the highest level of TG reduction in the gemcabene monotherapy analyses and dose response curve data from studies that assess gemcabene over across the full dose range;
- Gemcabene has a U-shaped TG dose response curve in hypertriglyceridemia subjects and including 600 mg along with 300 mg may further elucidate the mechanism;
- Gemcabene 600 mg is the proposed dose for the treatment of hypercholesterolemia and as such its effects in severe hypertriglyceridemia are being evaluated;
- Although TG lowering is mitigated at gemcabene 600 mg in hypertriglyceridemia subjects, LDL-C is significantly lowered at the 600 mg dose by a median % change of 17% ($p = 0.026$), unlike an increase of 8% ($p = 0.076$) at the 300 mg dose;
- Decreases in ApoB were observed across all doses.

Study 1027-04

In a pre-specified analysis in subjects with baseline TG ≥ 200 mg/dL (Study 1027-04) gemcabene lowered TG by a median % change at 12 weeks of 27% (p value for treatment difference < 0.05), 39% (p value for treatment difference < 0.01), 13% (p value for treatment difference = 0.623), and 9% (p value for treatment difference = 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 150 mg 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 subjects with isolated hypertriglyceridemia when TG levels are lowered. LDL-C elevation may be observed when triglyceride-rich VLDL lipolysis is facilitated as LDL are the metabolic product of VLDL catabolism.[4] In study 1027-04, non-significant increases in LDL-C of 16% and 8% at 150 mg and 300 mg and significant lowering in LDL-C of 17% (p value for treatment difference = 0.026) and 23% (p value for treatment difference < 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 gemcabene is facilitating the formation of larger less atherogenic LDL particles, supported by a lowering of ApoB across all doses.

Retrospective Integrated Analysis of Gemcabene Monotherapy

A retrospective integrated analysis of the effect of gemcabene monotherapy on TG in subjects with baseline TG ≥ 200 mg/dL included studies 1027-04 (low HDL), 1027-14 (healthy obese) and 4141001 (hypercholesterolemic).

Gemcabene monotherapy subjects with baseline TG ≥ 200 mg/dL had a difference median % lowering in TG of 25% (p value for treatment difference = 0.0192) and 32% (p value for treatment difference = 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.

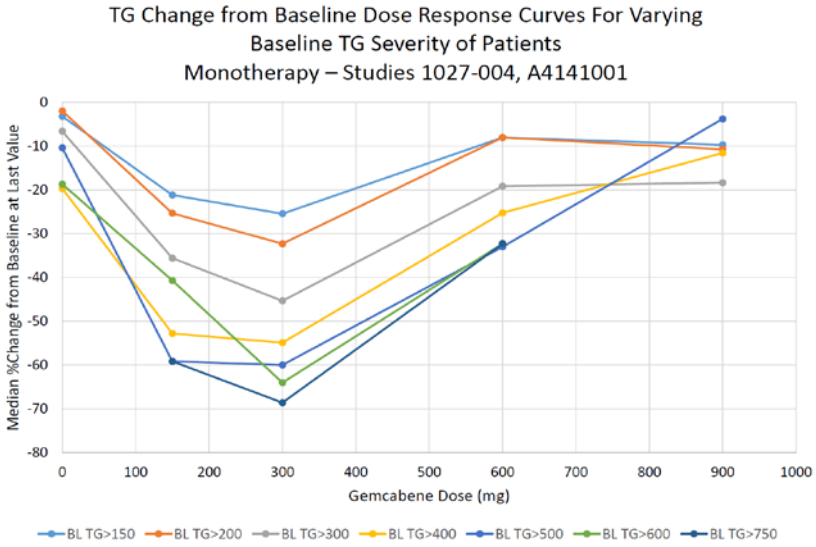
A further sub-cut of subjects with baseline TG ≥ 400 mg/dL yielded enough subjects to perform an analysis in subjects similar to those at risk for pancreatitis and representative of subjects to be enrolled in GEM-401. In this integrated analysis, subjects with TG ≥ 400 mg/dL on gemcabene 300 mg (n = 8) lowered TG by in median % change of 55% (p value for treatment difference = 0.0228), compared to a lowering of 20% for placebo (n = 6). Clinically significant, statistically non-significant TG lowering was observed for the gemacbene 150 mg and 600 mg. Clinically non-significant, statistically non-significant TG lowering was observed for gemcabene 900 mg.

Retrospective Integrated Analysis of Gemcabene Combined with Statin Therapy

The effect of gemcabene as add-on or combination to statin therapy was also analyzed (1027-18; 4141001 [atorvastain combination arms]) in subjects with baseline TG ≥ 200 mg/dL. Gemcabene had a median % lowering in TG similar to monotherapy: 38% (p value for treatment difference = 0.0067) for gemcabene 300 mg + statin (n = 23), compared to a lowering of 19% with statin alone (n = 26). There were no subjects in the dataset with baseline TG ≥ 400 mg/dL.

Dose Response Curve over Full Dose Range

In ONLY those studies that assessed gemcabene *over its full dose range* (1027-04 and A4141001), consistent TG dose effects were observed across all sub-cuts of baseline TG, with peak lowering at the gemcabene 300 mg dose.



In hypertrigyceridemic subjects, monotherapy gemcabene produces a U-shaped TG-lowering curve over its dose range. In subjects with baseline TGs ≥ 500 mg/dL gemcabene 300 mg lowers TG 50-60%. The effect on TG is less at doses lower and higher than 300 mg, approximately 30% with gemcabene 600 mg and 5% with gemcabene 900 mg. Importantly, beneficial effect on

TG are still observed at the 600 mg dose in all hypertriglyceridemic populations. This waning in TG effect at the higher doses may be explained by the shift in the balance between the ApoE and ApoC proteins. TG–rich particles are cleared through remnant receptors which is mediated by a balance between the levels of ApoE and the ApoC proteins on the particle. ApoE facilitates clearance, while the apo C's inhibit clearance. High level of ApoC-I, Apo C-II or ApoC-III appear to mask apo E, preventing it from recognizing /interacting with the remnant receptor, while allowing the particle to undergo lipolysis in the circulation. However, too much ApoC-III prevents intravascular lipolysis by inhibiting lipoprotein lipase (LPL) and too little ApoC-II prevents adequate activation of LPL. Therefore, an optimal balance of ApoC-II to ApoC-III, and between ApoE and the ApoC proteins are needed to be achieve optimal lipolysis of the TG-rich particle and clearance of its remnant.[5-8] Preclinical data shows gemcabene lowers both ApoC-II and apo C-III, supporting enhanced ApoC-II reduction in humans at the higher gemcabene dose (600 and 900 mg), which results in a reduction of optimal TG clearance via inhibition of LPL activation.[1] The gemcabene 600 mg dose in the current study will enhance the understanding of the effects of gemcabene on ApoC-II and ApoC-III and ultimately TGs.

1.3 Population Overview and Rationale

Hypertriglyceridemia is a common condition present in about a third of the population. It is well established that severe HTG, defined as TG levels ≥ 500 mg/dL (≥ 5.65 mmol/L) can significantly increases the risk of acute pancreatitis, and controlling TG levels to well below 500 mg/dL can effectively prevent the risk of its recurrence. [9, 10, 11]

In subjects with severe or very severe hypertriglyceridemia, fibrates, omega-3 fatty acids (OMG-3) and occasionally niacin are first-line therapy.

Niacin lowers TG and increases HDL-C levels in subjects with TG > 500 mg/dL. At doses of 500 to 2000 mg/day, niacin lowers TG by 10–30%, increases HDL-C by 10–40%, and lowers LDL-C by 5–20%.[12,13] 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 subjects with diabetes, chronic kidney disease, or uncontrolled hypothyroidism.[14]

Fibrates decrease TG levels by 30–50% and sometimes increase HDL-C levels in subjects with TG > 500 mg/dL.[15] In subjects 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 creatinine kinase (CK). Fibrates are contraindicated in subjects with liver and gall bladder disease and should be used with caution in renal insufficiency. Gemfibrozil (unlike fenofibrate) inhibits multiple glucuronosyltransferases, which can lead to reduced statin excretion and increased risk for myopathy and rhabdomyolysis.[15]

Omega-3 compounds are used in the treatment of subjects with TG > 500 mg/dL. To achieve a TG reduction of 20–50%, administration of 3–4 g/d of EPA plus DHA given in multiple capsules is required.[12] As with fibrates, with the reductions of TG levels there can be increased levels of LDL-C. Most common side effects include fishy taste and burping with no increased in adverse effects reported for statin and OMG-3 co-administration.[16]

Background statin therapy is increasingly common in subjects with moderate to severe hypertriglyceridemia due to increased cardiovascular risk in subjects with moderate hypertriglyceridemia and has become standard of care in diabetic subjects across all severities of hypertriglyceridemia. Therefore, a robust safety profile for TG-lowering compounds in combination with statins for these subjects is a necessity.[12] However, current lipid lowering agents are not ideal due to their limited TG-lowering effects and the potential for safety and tolerance issues, specifically in combination with statins.

Gemcabene has shown TG lowering from 20 to > 50% based on dose and severity of hypertriglyceridemia. To date, gemcabene has been shown to be generally well tolerated in combination with statins, with no drug interaction identified with either high-intensity simvastatin or atorvastatin. The current study assesses the efficacy and safety of gemcabene 300 mg and 600 mg in subjects with moderate to severe hypertriglyceridemia (TG ≥ 500 mg/dL to < 1500 mg/dL) who may or may not be receiving background statin therapy (± ezetimibe 10 mg) and who may or may not have Type 2 diabetes, a population representative of those hypertriglyceridemic subjects at risk for pancreatitis.

1.4 Risk/Benefit

The clinical program conducted to date has demonstrated that gemcabene is generally well tolerated. A total of 895 healthy adult subjects and subjects with various underlying conditions (including dyslipidemia, osteoarthritis, and hypertension) have been exposed to a minimum of at least 1 dose of gemcabene at doses ranging from 150 mg to 1500 mg QD. This includes 837 subjects who received multiple doses of up to 900 mg for up to 12 weeks. This also includes 292 subjects (150 subjects on high-intensity) on gemcabene in combination with a statin. Safety of these subjects 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 subjects (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 2 to 4 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 subject. 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 2 weeks of cessation of gemcabene, suggesting a vascular effect and not renal injury.

Based on data in 94 hypertriglyceridemic subjects (TG ≥ 200 mg/dL) in the 1027-04 protocol, the 300 mg dose of gemcabene showed the greatest TG effect (median percent change of -38.9% [$p<0.001$]). The current study (GEM-401) will assess the efficacy, safety and tolerability of gemcabene 300 mg and 600 mg in subjects with SHTG (TG ≥ 500 to < 1500 mg/dL) either on background statin therapy or statin naive with or without ezetimibe.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to assess the effect of gemcabene 300 mg and 600 mg QD compared to placebo on fasting serum TG levels after 12 weeks of treatment in subjects with severe hypertriglyceridemia (≥ 500 mg/dL to < 1500 mg/dL) on a self-reported, stable, heart-healthy diet.

2.1.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess the safety and tolerability of gemcabene 300 mg and 600 mg QD in subjects with severe hypertriglyceridemia;
- To assess the effect of gemcabene 300 mg and 600 mg QD on other lipid and apolipoprotein parameters, high-sensitivity C-reactive protein (hsCRP), serum amyloid A (SAA), angiopoietin like 4 (ANGPTL4), adiponectin, and fibrinogen after 12 weeks of treatment.

2.1.3 Exploratory Objectives

The exploratory objectives are the following:

[redacted]

2.2 Endpoints

2.2.1 Primary Endpoint

The primary efficacy endpoint is the percent change in fasting serum TG from baseline to EOS. Baseline will be defined as the average of the (Screening Visits [S1 and S2] or [S2 and S3] occurring up to 28 days prior to Study Day 1) and Study Day 1 [pre-dose]) values. EOS will be defined as the average of Week 10 (T4) and Week 12 (T5).

2.2.2 Secondary Efficacy Endpoints

The secondary endpoints are as follows:

- Change and percent change from baseline to Weeks 2, 6, 10 and 12 in fasting serum TG, and change from baseline to EOS in fasting serum TG;

- Change and percent change from baseline to Weeks 2, 6, 10, 12 and EOS in total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), HDL-C, and VLDL-C;
- Change and percent change from baseline to Weeks 10, 12 and EOS in Apo B, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, and ApoE;
- Change and percent change from baseline to Weeks 10, 12 and EOS in LDL-C (ultracentrifugation), LDL-TG, VLDL-TG, HDL-TG;
- Change and percent change from baseline to Week 12 in lipoprotein size and particle number (NMR), and ANGPTL4;
- Change and percent change from baseline to Weeks 10, 12 and EOS in hsCRP, IL-6, serum amyloid A (SAA), and fibrinogen;
- Percent of subjects achieving a TG value < 500 mg/dL (5.65 mmol/L) at Weeks 10, 12, and EOS.

2.2.3 Exploratory Endpoints

The exploratory efficacy endpoints are as follows:

- CI [redacted]

2.2.4 Secondary Safety Endpoints

Secondary endpoints related to safety include adverse events, safety laboratory parameters (chemistry including cystatin-C, hematology, coagulation values); urinalysis including urine protein:creatinine ratio, urine albumin:creatinine ratio and neutrophil gelatinase-associated lipocalin; vital signs, electrocardiogram (ECG) results; and physical examinations (PEs).

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2, randomized, double-blind, parallel-group, multi-center study. Subjects may enter the study with or without stable statin therapy, with or without ezetimibe (10 mg QD), and with or without diabetes, for at least 4 weeks prior to the Screening Visit. Approximately 90 subjects with severe hypertriglyceridemia (TG ≥ 500 mg/dL to < 1500 mg/dL) will be enrolled into the study. Total study duration will be up to 26 weeks with 12 weeks of study drug treatment. The study will consist of a Pre-Screening Visit (only for subjects requiring a Wash-Out Period), up to 3 Screening Visits (to stabilize diet and lifestyle and determine TG levels), a 12-week Treatment Period (with 5 Visits), and a Follow-up Visit (4 weeks after the last dose).

Pre-Screening (Wash-Out Period): A Wash-Out Period will be required for potential subjects taking any lipid-regulating therapies or supplements, with the exception of statins or ezetimibe 10 mg QD. Subjects may initiate the Wash-Out Period, if meeting all other criteria and have a qualifying fasting TG value of ≥ 350 mg/dL. For subjects requiring a Wash-Out Period, the Pre-Screening Visit will be their first study visit and will occur anywhere from 4 to 8 weeks prior to the Screening Visit (S1, Week -4to -2) based on the type of lipid-regulating therapy and its associated duration of wash-out required.

Subjects currently taking lipid-altering medications such as: niacin > 200 mg/day, fibrates, prescription or over-the-counter fish oil or other products containing omega-3 fatty acids (OMG-3), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, bile acid sequestrants, or other herbal products or dietary supplements with potential lipid-altering effects, must be able to safely discontinue therapy at the Pre-Screening Visit. The duration of the Wash-Out Period will be dependent upon the status of the subject's current lipid-regulating therapy. Specifically, PCSK9 inhibitors will require an 8-week Wash-Out Period, fibrates will require a 6-week Wash-Out Period, and niacin, OMG-3 compounds, bile acid sequestrants or other lipid-regulating therapies will require a 4-week Wash-Out Period prior to the Screening Visit. If the subject needs to be washed off more than one lipid-altering medication; the medication that requires the longest Wash-Out Period will be the default. For example, if a subject is taking OMG-3 and fibrates, then the subject would undergo a six-week Wash-Out Period. Exception: if a potential subject is statin-naïve, or dosing only on a statin or ezetimibe (for at least 12 weeks) and not currently dosing on other lipid-altering medications, there is no requirement for a Pre-Screening Visit.

During this Wash-Out Period, potential subjects will be counseled on the importance of maintaining a heart-healthy diet and limiting alcohol intake.

Screening Period: This is the TG qualifying period. All potential subjects will participate in the Screening Period, including Screening Visit 1 (S1), Screening Visit 2 (S2) and, if necessary as outlined below, optional Screening Visit 3 (S3) up to 28 days prior to Study Day 1 (Visit T1). For potential subjects on stable statin therapy and/or ezetimibe for ≥12 weeks and who do not require a Wash-Out Period, S1 will be their first study visit. For other subjects who have been washing out their other lipid medications, S1 occurs after the full required washout has been completed.

During this Screening Period, potential subjects must meet the TG qualifying values in order to be eligible for randomization on Day 1 (Visit T1).

The screening visits can be completed up to 28 days but not less than 14 days prior to T1 (Day 1). The visits are provided with recommended timepoints; however, the minimum time between visits can be as short as 1 week with the Screening Period as short as 14 days for qualification with S1 and S2 visits or 21 days for qualification with S2 and S3. At the end of this 2-4-week diet and lifestyle stabilization and TG qualifying period, eligible subjects must have an average fasting TG level ≥ 500 mg/dL to < 1500 mg/dL in order to qualify for the 12-week double-blind treatment period. The TG level for qualification will be based on the average (arithmetic mean) of the Visit S1 and Visit S2 values. If a subject's average TG level from Visit S1 and Visit S2 falls outside the required range for entry into the study, one additional sample for fasting TG value can be collected 1 week later (at the Optional Visit S3), and the arithmetic mean from Visits S2 and S3 will then be used to determine eligibility.

Double-Blind Treatment Period: After confirmation of qualifying fasting TG values and all other inclusion and exclusion criteria, eligible subjects will be randomized and enter a 12-week, double-blind treatment period. At Visit T1, 90 eligible subjects will be randomized via an interactive web/voice response system (IWRS/IVRS) on Study Day 1 in a 1:1:1 ratio (30 subjects per group) to one of the following treatment groups:

- Gemcabene 300 mg QD, or
- Gemcabene 600 mg QD, or
- Placebo

Subjects will be stratified by statin therapy (yes or no) and qualifying TG value (< 880 mg/dL or ≥ 880 mg/dL) to ensure background therapies and baseline TG values are balanced across all treatment groups.

The primary evaluation of efficacy will be at EOS (using the average of Week 10 [T4] and Week 12 [T5]). The Follow-up Visit (telephone call) will occur 4 weeks (± 3 days) after the last dose of study drug.

3.2 Study Indication(s)

Treatment with gemcabene is indicated as an adjunct to diet to reduce serum triglyceride (TG) levels in adult patients with severe hypertriglyceridemia (≥ 500 mg/dL); where lowering TG levels below 500 mg/dL may decrease a patient's risk for developing pancreatitis.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

1. Provision of written and signed informed consent (by subject or legal guardian) prior to any study-specific procedure;
2. Male or female ≥18 years of age at time of consent;
    a. Female subjects 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;
    b. 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. Double-barrier contraception is required; and
    c. Male subjects must agree to use contraception by means of a condom and may not donate sperm throughout the duration of the study and for 8 days after the last dose of study drug.
3. Currently on a self-reported, stable, low-fat, low-cholesterol diet and if on a stable dose of statins and/or ezetimibe (10 mg), statins and ezetimibe must be started at least 12 weeks prior to the Screening Visit;
4. Mean fasting TG value ≥ 500 mg/dL to < 1500 mg/dL (with the higher value no more than 50% greater than the lower value) from the S1 and S2 Visits (or alternatively S2 and S3);
5. Physical examination, including vital signs, that is within normal limits or clinically acceptable to the Investigator;
6. Weight ≥ 50 kg; with a body mass index (BMI) ≤ 45 kg/m²; and
7. Subjects with Type 2 diabetes who take anti-diabetes pharmacologic therapy must be on a stable a regimen for at least 3 months, with no planned changes in medications for the study duration.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study. Subjects may re-screen once if they were previously excluded from the study based on criteria that has now been altered by Amendment #3.

1. Known and previously documented homozygous genetic deficiencies (LPL, ApoC-II, ApoC-III, ApoA-V, GPIHBP1, or LMF1);
2. History of pancreatitis within the last 6 months prior to screening (Visit S1);

3. History of bariatric surgery; symptomatic gallstone disease, unless treated with cholecystectomy;
4. Abnormal liver function test at the Pre-Screening Visit or any of the Screening Visits (aspartate aminotransferase or alanine aminotransferase > 2 × the upper limit of normal [ULN], total bilirubin > 1.5 × ULN, or alkaline phosphatase > 2 × ULN based on appropriate age and gender normal values). Subjects with bilirubin > 1.5 × ULN and history of Gilbert's syndrome may be included; reflexive direct bilirubin testing will be used to confirm Gilbert's syndrome;
5. Creatine kinase (CK) at the Pre-Screening Visit or any of the Screening Visits > 3 × ULN and/or unexplained muscle pain, tenderness or weakness;
6. Active liver disease (e.g., cirrhosis, alcoholic liver disease, hepatitis B [HBV], hepatitis C [HCV], autoimmune hepatitis, liver failure, liver cancer), history of liver transplant, known diagnosis of human immunodeficiency virus (HIV), or acquired immune deficiency virus;
7. Moderate to severe renal insufficiency defined as an estimated GFR < 60 mL/min/1.73 m^2 (calculated using The Chronic Kidney Disease Epidemiology Collaboration equation) at the Pre-Screening Visit or at any of the Screening Visits;
8. Abnormal urinalysis (defined as proteinuria ≥ 1+ or any male or non-menstruating female with ≥ 1+ hematuria), with a confirmatory abnormal urine protein:creatinine ratio (e.g., ≥ 1+ proteinurea or hematuria without confirmation by abnormal protein:creatinine ratio will not be an exclusion);
9. Uncontrolled thyroid disease: hyperthyroidism or hypothyroidism as defined by thyroid-stimulating hormone (TSH) below the lower limit of normal or > 1.5 × ULN, respectively, based on results from the Pre-Screening Visit or the Screening Visit. If controlled, treatment should be stable for at least 3 months prior to the Screening Visit;
10. Type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus HbA1c value > 9.5% based on results from the Pre-Screening Visit or the Screening Visit), or any diabetic subject taking a thiazolidinedione (e.g., pioglitazone, rosiglitazone);
11. New York Heart Association Class III or IV heart failure (see Appendix C);
12. Myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, or other major cardiovascular events resulting in hospitalization within 3 months of the Screening Visit (S1). Subjects with adequately treated stable angina, per Investigator assessment, may be included;
13. Uncontrolled cardiac arrhythmia or prolonged QT on the Screening Visit or Study 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;
14. Uncontrolled hypertension, defined as sitting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg, and confirmed by repeat measurement;

15. Currently receiving cancer treatment(s) or, in the Investigator's opinion, at risk of relapse for recent cancer;
16. Inadequate washout of a PCSK9 inhibitor (8 weeks prior to the Screening Visit S1), a fibrate lipid lowering agent (6 weeks prior to the Screening Visit S1), niacin > 200 mg/day, OMG-3, bile acid sequestrants or other lipid lowering therapies (4 weeks prior to the Screening Visit S1);
17. Use of any excluded medications or supplements within 3 months prior to S1 (e.g., follow label restrictions for any concomitant medications including statins, see Appendix D for a reference list of cytochrome P450 [CYP] 3A4 inhibitors);
18. Hypersensitivity to or a history of significant adverse reactions to any fibrate lipid regulating agent;
19. History of drug or alcohol abuse within the past year or inability to comply with protocol requirements, including subject alcohol restrictions (see Section 5.6.3);
20. Previously treated with gemcabene (i.e., CI-1027); participation in another clinical study of an investigational agent or device concurrently or within 1 month prior to the Screening Visit, or use of an investigational agent within 1 month or 5 half-lives (if known), whichever is longer, prior to the Screening Visit; or
21. Any other finding which, in the opinion of the Investigator, would compromise the subject's safety or participation in the study.

4.3 Withdrawal Criteria

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

- The subject withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance (ie, alert TG value ≥ 2000 mg/dL; 8.1.4.4) that exposes the subject to substantial risk and/or does not allow the subject 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 subject;
- Pregnancy;
- Requirement of a concomitant medication which is prohibited by the protocol;
- Subject failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or any regulatory authority(ies).

If a subject 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 subject withdrawal must be documented in the electronic Case Report Form (eCRF). When a subject withdraws due to a SAE, the SAE must be reported in accordance with the reporting requirements as defined.

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

Withdrawn subjects will not be replaced. The sample size calculation accounts for a 15% dropout rate in the study.

5 STUDY TREATMENTS

5.1 Treatment Groups

Ninety subjects will be randomized on Study Day 1 in a 1:1:1 ratio to the following treatment groups: placebo or gemcabene 300 mg or gemcabene 600 mg. Subjects may be on a stable statin regimen as appropriate, with or without ezetimibe 10 mg QD for at least 12 weeks prior to the Screening Visit. Subjects will be stratified by baseline statin therapy (yes or no) and qualifying TG value (< 880 mg/dL or ≥ 880 mg/dL).

5.2 Dose Rationale

Based on a prospective analysis in a gemcabene monotherapy study (1027-04) in subjects with mild-moderate hypertriglyceridemia (TG ≥ 200 mg/dL) and a retrospective integrated analysis of all studies (1027-04, 1027-14 [healthy, obese subjects], and 4141001 [hyperlipidemia subjects +/- atorvastatin]) that tested gemcabene monotherapy in subjects with mild to severe hypertriglyceridemia, we conclude that the 300 mg QD dose is optimal based on monotherapy data. The 600 mg dose will also be included in the GEM-401 protocol for the following reasons: gemcabene 600 mg is the proposed dose for the treatment of hypercholesterolemia and as such its effects in severe hypertriglyceridemia need to be understood; gemcabene has a U-shaped TG dose response curve in Type IV subjects and further study with gemcabene 600 mg may further elucidate the mechanism; although TG lowering is mitigated at gemcabene 600 mg in hypertriglyceridemia subjects, LDL-C is significantly lowered at the 600 mg dose by a median % change of 17% ($p = 0.026$), unlike an increase of 8% ($p = 0.076$) at the 300 mg dose. Non-significant decreases in ApoB were observed at all doses. Therefore, we propose including the 300 mg and 600 mg dose in our Phase 2 study to assess efficacy, safety and tolerability in severe hypertriglyceridemia (TG ≥ 500 mg/dL to < 1500 mg/dL) prior to Phase 3.

5.3 Randomization and Blinding

Subjects who have completed the Screening Visit and meet all of the inclusion and none of exclusion criteria will be randomized into the study on Study Day 1. Randomized treatment assignment and randomization numbers will be assigned via IWRS/IVRS. Following randomization, study drug will be dispensed in a double-blind manner. The Sponsor and all clinical site personnel (Investigator, pharmacist, etc.) will be blinded to the treatment group for each subject. Subjects also will be blinded to the treatment they receive.

5.4 Breaking the Blind

Blinding is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of subject safety. The Investigator should contact the Medical Monitor who will break the blind in a qualifying event. When the blind is broken, the reason must be fully documented.

5.5 Drug Supplies

5.5.1 Study Drug Identification

Established names	Gemcabene calcium – parent gemcabene
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 - parent 6,6'-oxybis(2,2-dimethylhexanoicacid)
Molecular formula	$C_{16}H_{28}O_5 \cdot Ca$ – parent $C_{16}H_{30}O_5$
Molecular weight	340.48 – parent 302.408
Drug name/formulation/amount	Gemcabene (parent)/tablets/300 mg
Manufacturer (drug substance)	CI [redacted]
Manufacturer (drug product, placebo)	CI [redacted]
Storage requirements	Room temperature (15 to 30°C) in a secured location (locked) with no access for unauthorized personnel.

5.5.2 Formulation and Packaging

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: CI [redacted]

A matching placebo tablet is available. The matching placebo tablet contains CI [redacted]

Study drug will be double-blinded and prepared in bottles with 30 days of dosing contained within each bottle. The subjects will be asked to take one tablet from each of the 2 bottles for a total of 2 tablets per day as outlined below:

- 300 mg: 30 gemcabene tablets in one bottle + 30 matching placebo tablet in a second bottle
- 600 mg: 2 bottles each containing 30 300 mg gemcabene tablets
- Placebo: 2 bottles each containing 30 placebo tablets.

5.5.3 Study Drug Preparation and Dispensing

Study drug will be administered at the site on clinic visit days. Subjects will receive a study drug kit comprised of two bottles, labeled Bottle A and Bottle B. Subjects must take one tablet from each bottle every day. In no case should the subject take two tablets from the same bottle on a given day. Subjects will self-dose at all other times during the Treatment Period. The Investigator or designee will provide subjects with sufficient study drug until the next scheduled study visit.

5.5.4 Study Drug Administration

The first dose of study drug will be administered at the site on Study Day 1. On days with a scheduled office visit with blood sample collection, subject will remain fasted and should not take gemcabene until after the blood samples are collected at the site. On all other days, the subject will self-dose: taking study drug at the same time in the morning with a full glass (8 ounces) of water either with or without food. If a subject misses a dose prior to 6:00 PM, then the subject should take their dose. However, if past 6:00 PM, the subject should not dose and then count the dose as a "missed dose." The subject will resume normal dosing the next day (i.e., do not take two doses the following day).

5.5.5 Treatment Compliance

Subjects 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-randomization during the Treatment Period and at the Early Termination Visit, if applicable, and recorded on the appropriate eCRF and the drug accountability log.

The Investigator or designee will remind subjects 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.

5.5.6 Storage and Accountability

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

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). If a site does not have appropriate SOPs for compliance, the study drug will be returned to the Sponsor at the end of the study.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Permitted Medications and/or Procedures

Subjects are required to be on a stable, heart-healthy diet. Randomized subjects should remain on previously prescribed background stable statins or ezetimibe 10 mg QD for the duration of the study, if started at least 12 weeks prior to the Screening visit. Subjects with Type 2 diabetes who receive pharmacologic treatment must be on a stable regimen for 3 months prior to signing informed consent at the Screening Visit (S2). It is strongly recommended that subjects with Type 2 diabetes be under routine care for management and monitoring of their diabetes.

5.6.2 Excluded Medications and/or Procedures

Subjects are not permitted to receive treatment with a PCSK9 inhibitor (8 weeks prior to the Screening Visit), a fibrate lipid-regulating agent (6 weeks prior to the Screening Visit), niacin (4 weeks prior to the Screening Visit), or other lipid-regulating therapies such as bile acid sequestrants and OMG-3 compounds (4 weeks prior to the Screening Visit). If subjects have a confirmed TG alert value of > 2000 mg/dL they should follow the steps in Section 8.1.4.4 which may require the subject to stop study treatment and begin TG-lowering rescue medication including OMG-3 compounds and/or fibrates. Subjects are not permitted the use of tamoxifen, estrogens or progestins that have not been stable for > 4 weeks prior to the Screening Visit (S1), nor the use of oral or injected corticosteroids or anabolic steroids.

Subjects are instructed to follow the package label for all concomitant medications, including statins. See Appendix D for a reference list of CYP3A4 inhibitors.

5.6.3 Restrictions and Dietary Guidelines

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

Subjects are restricted from using alcohol within 48 hours prior to study visits. Subjects must not drink more than 2 units of alcohol per day. A unit of alcohol is defined as a 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;

All clinic visit assessments require subjects to fast. This is defined as no food or caloric beverages for at least 10 hours prior to sample collection. Subjects will be permitted to have water, black tea or black coffee.

On all other days, the subject will self-dose: taking study drug at the same time in the morning with a full glass (8 ounces) of water either with or without food.

Subjects will maintain a stable, heart-healthy diet (counselled per NCEP ATP-III guidelines or equivalent) throughout the study.

5.6.4 Documentation of Prior/Concomitant Medication Use and Procedures

A concomitant medication is any treatment including nutritional supplements, vitamins, or over-the-counter medications received by or prescribed to the subject concomitantly to the study, from the time of informed consent to the Follow-up Visit or the ET Visit, if applicable. Concomitant Procedures are procedures (i.e. tooth extraction, CT scan), and NOT the clinically relevant diagnosis that precipitated the procedure.

The Investigator should record the use of all concomitant medications taken during the study, both prescribed and over the counter, in the eCRF and the source document. This includes drugs used on a chronic and as needed basis. Subjects 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. Concomitant procedures will be documented on the Concomitant Medication CRF and the reason for the procedure (i.e. diagnosis) will be documented on the Medical History or Adverse Event CRF, whichever is appropriate.

6 STUDY PROCEDURES

A tabular listing of the Schedule of Procedures can be found in Appendix A. ALL CLINIC VISITS REQUIRE THAT THE SUBJECT IS IN A FASTED STATE. This is defined as no food or caloric beverage for at least 10 hours prior to sample collection. Subjects will be permitted to have water, black tea or black coffee.

6.1 Informed Consent

Written informed consent for the study will be obtained from all subjects before any protocol-specific procedures are performed. See Section 11.3 for details on informed consent.

6.2 Pre-Screening Visit

Only subjects requiring a Wash-Out Period will participate in the Pre-Screening Visit.

Subjects must have a Pre-Screening TG value ≥ 350 mg/dL and < 1800 mg/dL before washing out of current TG-lowering therapies and proceeding to S1.

A Wash-Out Period will be required for eligible subjects taking any lipid-regulating therapies or supplements, with the exception of statins or ezetimibe. For subjects 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. Specifically, PCSK9 inhibitors will require an 8-week Wash-Out Period, fibrates will require a 6-week Wash-Out Period, and niacin, OMG-3, bile acid sequestrants or other lipid-regulating therapies will require a 4-week Wash-Out Period prior to the Screening Visit. If the subject needs to be washed off more than one lipid-altering medication; the medication that requires the longest Wash-Out Period will be the default. For example, if a subject is taking OMG-3 and fibrates, then the subject would undergo a six-week Wash-Out Period.

The Wash-Out Period will only be initiated after inclusionary lab values are received and reviewed.

The following procedures will be performed at the Pre-Screening Visit:

- Obtain informed consent;
- Conduct eligibility assessment based on inclusion/exclusion criteria;
- Obtain medical/surgical history and demographics;
- Obtain concomitant medications; including all anti-diabetes pharmacologic therapy for subjects with Type 2 diabetes
- Perform full physical examination;
- Record vital signs, height, weight and calculate BMI;
- Collect urine sample;
- Perform urine pregnancy test (for women of child-bearing potential only);
- Obtain blood sample for the following:

- Safety chemistry panel, coagulation, and hematology;
- TSH, HbA1c, and serology (HBV, HCV, and HIV); and
- Fasting serum TG only;

- Explain importance of continued adherence to a stable, heart-healthy diet and limited alcohol intake;
- Initiate wash-out; and
- Assess adverse events (AEs 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 eCRF) and concomitant medications.

6.3 Screening Visits

The screening visits can be completed up to 28 days but not less than 14 days prior to T1 (Day 1). The visits are provided with recommended timepoints; however the minimum time between visits can be as short as 1 week with the screening period as short as 14 days for qualification with S1 and S2 visits or 21 days for qualification with S2 and S3.

To qualify for randomization into the treatment period, the mean of TG value at Visits S1 and S2 must be ≥ 500 mg/dL (5.65 mmol/L) to < 1500 mg/dL (16.95 mmol/L) with the greater value not more than 50% of the lower value. If the mean of TG values at Visits S1 and S2 is < 500 mg/dL or ≥ 1500 mg/dL or outside the 50% range in variability, the subject can be brought in for an additional TG value (lipid profile) one week later at Week -1 (Screening Visit S3). If the mean of TG values at Visits S2 and S3 is < 500 mg/dL or ≥ 1500 mg/dL or outside the 50% range in variability, then the subject will be a screen failure.

Subjects who are a screen failure may not re-screen at any time.

If all of the inclusion criteria (Section 4.1) are met and the subject has none of the exclusion criteria (Section 4.2) the subject may be randomized into the 12-week treatment period.

6.3.1 Screening Visit 1 (up to Day -28 to -14/Week -4 or -2)

Only those subjects NOT requiring wash-out from PCSK9 inhibitors, fibrates, niacin, OMG-3 or bile-acid sequestrants may participate in Screening Visit 1. Subjects may be receiving statins (± ezetimibe 10 mg) only if therapy is stable for ≥ 12 weeks prior to Screening Visit 1.

Subjects must have S1 TG value ≥ 425 mg/dL and < 1800 mg/dL before proceeding to S2.

For subjects 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, HbA1c, and serology (HBV, HCV, and HIV). Updates, as needed, will be made to medical/surgical history, demographics, and concomitant medications.

The following procedures will be performed at the Screening Visit (up to Day -28):

- Obtain informed consent;
- Confirm eligibility based on inclusion/exclusion criteria;
- Obtain medical/surgical history and demographics;
- Obtain concomitant medications; including all anti-diabetes pharmacologic therapy for subjects with Type 2 diabetes;
- Perform full physical examination;
- Perform symptom-directed physical examination (only for subjects who required a Wash-Out Period and completed the full physical examination at the Pre-Screening Visit);
- Record vital signs, height, weight and BMI;
- Collect urine sample;
- Perform serum pregnancy test (for women of child-bearing potential only);
- Obtain blood sample for the following:
  - Safety chemistry panel, coagulation, and hematology;
  - TSH, HbA1c, and serology (HBV, HCV, and HIV); and
  - Fasting lipid panel;
- Perform 12-lead ECG;
- Explain importance of continued adherence to a stable, heart-healthy diet and limited alcohol intake; and
- Assess adverse events (AEs 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 eCRF) and concomitant medications.

6.3.2 Screening Visit 2 (up to Day -14 or -7/Week -2 or -1)

All subjects determined as eligible as per the assessments at Screening Visit 1 and with a TG value ≥ 425 mg/dL and < 1800 mg/dL will participate in the Screening Visit 2.

The following procedures will be performed at the Screening Visit 2 (up to Day -14):

- Confirm eligibility based on inclusion/exclusion criteria;
- Update medical/surgical history and demographics;
- Update concomitant medications;
- Record vital signs and weight;
- Obtain blood sample for the following:
  - Fasting lipid panel;
  - Safety chemistry panel, coagulation, and hematology;

- Explain importance of continued adherence to a stable, heart-healthy diet and limited alcohol intake; and
- Assess adverse events (SAEs 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 eCRF) and concomitant medications.

6.3.3 Optional Screening Visit 3 (up to Day -7/Week -1)

All subjects determined as eligible as per the assessments at Screening Visit 2 (with the exception of TG) may participate in the Screening Visit 3.

The following procedures will be performed at the Screening Visit 3 (up to Day -7):

- Confirm eligibility based on inclusion/exclusion criteria;
- Update medical/surgical history and demographics;
- Update concomitant medications;
- Record vital signs and weight;
- Obtain blood sample for the following:
  - Safety chemistry panel, coagulation, and hematology;
  - Fasting lipid panel;
- Explain importance of continued adherence to a stable, heart-healthy diet and limited alcohol intake; and
- Assess adverse events (SAEs 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 eCRF) and concomitant medications.

6.4 Treatment Period (Visit T1 through Visit T5)

6.4.1 Visit T1 (Study Day 1)

The following procedures will be performed pre-dose at Visit T1 (Study Day 1):

- Perform symptom-directed physical examination;
- Determine if there have been any changes in the subject's health affecting eligibility;
- Record vital signs, weight and waist circumference;
- Collect urine sample;
- Perform urine pregnancy test (for women of child-bearing potential only);
- Obtain blood sample for the following:
  - Safety chemistry panel, coagulation, and hematology;
  - Fasting lipid panel; LDL ultracentrifugation, and apolipoproteins;

  - Fasting lipoprotein size and number (NMR);
  - Fasting insulin and FPG;
  - HbA1c;
  - hsCRP, IL-6, SAA, ANGPTL4, adiponectin, and fibrinogen
  - Cystatin-C;
  - Genotype reserve sample; and
  - Serum and plasma reserve samples.
- Perform 12-lead ECG;
- Randomize subjects via IVRS/IWRS;
- Dispense study drug and instructions;
- Explain importance of continued adherence to a stable, heart-healthy diet and limited alcohol intake;
- Distribute subject dose diary;
- Assess adverse events and update concomitant medications; and
- Administer study drug (study drug will be administered at the site on Study Day 1).

6.4.2 Visit T2 (Week 2)

The following procedures will be performed at Visit T2 (Week 2/Day 15 ±3 days):

- Perform symptom-directed physical examination;
- Record vital signs and weight;
- Perform urine pregnancy test (for women of child-bearing potential only);
- Obtain blood sample for the following:
  - Safety chemistry panel, coagulation, and hematology;
  - Fasting lipid panel; and
  - Serum and plasma pharmacokinetic (PK) reserve samples.
- Perform 12-lead ECG;
- Assess and document study drug compliance;
- Dispense study drug and instructions;
- Collect subject dose diary;
- Distribute subject dose diary;
- Assess adverse events and update concomitant medications; and

- Administer study drug (subjects will self-dose).

6.4.3 Visit T3 (Week 6)

The following procedures will be performed at Visit T3 (Week 6/Day 43 ±3 days):

- Perform symptom-directed physical examination;
- Record vital signs and weight;
- Collect urine sample;
- Perform urine pregnancy test (for women of child-bearing potential only);
- Obtain blood sample for the following:
  - Safety chemistry panel, coagulation, and hematology;
  - Fasting lipid panel; and
  - Serum and plasma PK reserve samples;
- Perform 12-lead ECG;
- Assess and document study drug compliance;
- Dispense study drug and instructions;
- Explain importance of continued adherence to a stable, heart-healthy diet and limited alcohol intake;
- Collect subject dose diary;
- Distribute subject dose diary;
- Assess adverse events and update concomitant medications; and
- Administer study drug (subjects will self-dose).

6.4.4 Visit T4 (Week 10)

The following procedures will be performed at Visit T4 (Week 10/Day 71 ±3 days):

- Perform symptom directed physical examination;
- Record vital signs and weight;
- Perform urine pregnancy test (for women of child-bearing potential only);
- Obtain blood sample for the following:
  - Safety chemistry panel, coagulation, and hematology;
  - Fasting lipid panel, LDL-C ultracentrifugaton, apolipoproteins;
  - hsCRP, IL-6, SAA, and fibrinogen;
  - Reserve serum and PK plasma samples;

- Perform 12-lead ECG;
- Assess and document study drug compliance;
- Explain importance of continued adherence to a stable, heart-healthy diet and limited alcohol intake;
- Collect subject dose diary;
- Distribute subject dose diary;
- Assess adverse events and update concomitant medications; and
- Administer study drug (subjects will self-dose).

6.4.5 Visit T5 (Week 12)

The following procedures will be performed at Visit T5 (Week 12/Study Day 85 [can be performed up to 3 days prior to Study Day 85, but not after Study Day 85]):

- Perform full physical examination;
- Record vital signs and weight;
- Collect urine sample;
- Perform serum pregnancy test (for women of child-bearing potential only);
- Obtain blood sample for the following:
  - Safety chemistry panel (clinically significant abnormal creatinine results at Week 12 will also be followed-up 2 weeks (±3 days) after the last dose of study drug in addition to the 4 week (±3 days) Follow-up Visit), coagulation, and hematology;
  - Fasting lipid panel, LDL-C ultracentrifugation, and apolipoproteins;
  - Fasting lipoprotein size and number (NMR);
  - Fasting insulin and FPG;
  - HbA1c;
  - hsCRP, IL-6, SAA, ANGPTL4, adiponectin, fibrinogen;
  - Cystatin-C;
  - Reserve serum and PK plasma samples;
- Perform 12-lead ECG;
- Assess and document study drug compliance;
- Collect subject dose diary;
- Assess adverse events and update concomitant medications.

6.5 Follow-up Visit (Week 16)

The Follow-up Visit will be conducted as a telephone call 4 weeks (±3 days) after the last dose of study drug, unless the subject requires a site visit due to an abnormal result at Week 12 (or the ET Visit, if applicable) or an ongoing treatment-related adverse event.

The following procedures will be performed at the Follow-up Visit (Week 16 ±3 days):

- Perform symptom-directed physical examination (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event);
- Collect urine sample for urinalysis including urine protein:creatinine ratio, albumin:creatinine ratio and NGAL (only for subjects who had an abnormal result at Week 16 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event);
- Obtain blood sample for safety chemistry panel, cystatin-C, coagulation, and hematology (only for subjects who had an abnormal result at Week 12[or the ET Visit, if applicable] or an ongoing treatment-related adverse event); and
- Assess adverse events and update concomitant medications.

6.6 Early Termination Visit and Withdrawal Procedures

For subjects who are withdrawn from the study prior to completion, the following procedures will be performed at the ET Visit:

- Perform full physical examination;
- Record vital signs and weight and waist circumference;
- Collect urine sample;
- Perform serum pregnancy test (for women of child-bearing potential only);
- Obtain blood sample for the following:
  - Safety chemistry panel, coagulation, and hematology;
  - Fasting lipid panel and apolipoproteins;
  - Fasting lipoprotein size and number (NMR);
  - Fasting insulin, and FPG;
  - HbA1c;
  - hsCRP, IL-6, SAA, ANGPTL4, adiponectin, and fibrinogen;
  - Cystatin-C;
  - Reserve serum and PK plasma samples;
- Perform 12-lead ECG;
- Assess and document study drug compliance;

- Collect subject dose diary; and
- Assess adverse events and update concomitant medications.

7 EFFICACY ASSESSMENTS

The following efficacy assessments will be measured in order to obtain the primary, secondary, and exploratory endpoints:

- Fasting TG, TC, HDL-C, non-HDL-C, VLDL-C at baseline, Week 2, Week 6, Week 10 and Week 12:
- Fasting LDL-C (ultracentrifugation), LDL-TG, VLDL-TG, HDL-TG at baseline, Week 10 and Week 12;
- Fasting total apolipoprotein B (ApoB), ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, and ApoE at baseline, Week 10 and Week 12;
- Fasting lipoprotein size and number (NMR), adiponectin, ANGPTL4 at baseline and Week 12;
- hsCRP, IL-6, SAA and fibrinogen at baseline, Week 10 and Week 12;
- CI [redacted]

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject 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 eCRF.

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). Subjects 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 eCRF. 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 eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. 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 eCRF. 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 eCRF.

Any medical condition already present prior to the subject 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 subject 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.

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than known therapeutic doses. Overdoses with associated symptoms are always handled as AEs and reported as such. Overdoses without associated symptoms are not reported as AEs but are documented in [specify eg, CRF] in order to collate information for the IB regarding the level of excess dosage taken or administered without adverse effects. An overdose will be reported irrespective of outcome even if toxic effects were not observed.

8.1.1 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.

8.1.2 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.

8.1.3 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 Investigator's assessment of causality must be provided for all AEs. The causality is the determination of whether there exists a reasonable possibility that the study drug itself (eg, gemcabene or placebo) caused or contributed to an AE.

If the final determination of causality is unknown and the Investigator does not know whether the study drug caused the event, then the event will be handled as "related to study drug" for reporting purposes. If the Investigator's causality is "unknown, but not related to study drug", this should be clearly documented on study records.

The relationship of an adverse event to the administration of the study drug will 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 subject may have.
- Concomitant drug -
  - The other drugs the subject is taking or the treatment the subject 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.

8.1.4 Specific Safety Measures

8.1.4.1 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 subject'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.

8.1.4.2 Creatinine increase

If, at any visit, a creatinine increase of > 0.3 mg/dL (27 µmol/L) from baseline, a GFR decrease of >15 mL/min from baseline, or a > 30 urinary albumin:creatine ratio mg/g is observed, a repeat chemistry/urinalysis will be performed. The subject'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.

During the study, clinically significant abnormal results in NGAL will be used as a means of identifying subjects who have unremarkable creatinine/BUN studies at the time of assessment but may require additional or closer/follow-up monitoring of renal parameters. Cystatin-C will be measured at baseline and Week 12.

8.1.4.3 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 E. For liver injury, laboratory data will be integrated with hepatic signs and symptoms. Alanine aminotransferase increases > 2 × ULN with symptoms of hepatitis or > 3 × ULN with or without symptoms of hepatitis will be evaluated and managed according to guidelines.

8.1.4.4 Increased risk for pancreatitis (TG ≥ 2000 mg/dL)

To prevent the risk for pancreatitis, lab alerts will be given for TG values ≥ 2000 mg/dL. A subject with a TG ≥ 2000 mg/dL should have a confirmatory TG value obtained within 1 week. As a first step, the subject should be immediately counseled and managed on their adherence to a heart-healthy diet, restricted alcohol intake and diabetic control. A follow-on TG value should be obtained 2 weeks later. If the TG remains ≥ 2000 mg/dL then the study medication should be stopped, and the subject should complete the ET visit and be instructed to begin TG-lowering rescue medication (fibrates and/or OMG-3 compounds).

8.2 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 subject 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 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 subject or subject 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.

8.3 Serious Adverse Event 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, the Sponsor or designee is to be notified within 24 hours of awareness of the event by the Investigator or designee.

All SAEs and follow-up information must be reported to the Sponsor or designee within 1 business day or 24 hours 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: PI

Facsimile: PI

E-mail: PI

In particular, if the SAE if fatal or life-threatening, notification to the Sponsor or designee must be made immediately, 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.

In the rare event that the Investigator does not become aware of the occurrence of a SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of their first awareness of the SAE.

8.4 Pregnancy Reporting

For investigational products within clinical studies, an Exposure In Utero occurs if:

- A female becomes, or is found to be pregnant after receiving the study drug (eg, after Study Day 1).

If a subject participating in the study becomes pregnant during their participation in the study or within 30 days of discontinuing study drug, the Investigator must report the pregnancy to PI Drug Safety within 24 hours of awareness on the Exposure In Utero form.

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

The Investigator will follow the subject until completion of the pregnancy or until pregnancy termination (ie, induced abortion) and notify PI Drug Safety of the pregnancy outcome. The Investigator will provide this information as a follow up to the initial EIU form. The reason(s) for an induced abortion should be specified. 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 SAE(s).

In the case of a live birth, the “normality” of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an EIU form can be completed). The “normality” of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion findings are suggestive of a congenital anomaly.

8.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA, applicable competent authorities concerned, and to the Central Ethics Committee concerned as soon as possible, but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

Expedited reporting of suspected unexpected serious adverse reactions related to non-investigational medical products (NIMPs) used in this study (e.g., simvastatin, atorvastatin, rosuvastatin, and/or ezetimibe) will not be necessary. Listings of the cases related to these NIMPs will be included in the Development Safety Update Report.

8.6 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 central laboratory for evaluation. Assessments that require a subject to fast will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Subjects will be permitted to have water, black tea or black coffee.

Central laboratory results will be provided to the sites, with the exception of the post-randomization lipid values. TG alert values with a risk mitigation plan is in place with the Central Laboratory (Section 8.1.4.4 Increased risk for pancreatitis [TG ≥ 2000 mg/dL]). Laboratory results that appear potentially spurious based on the Investigator's clinical assessment and review of the subject's medical history may be repeated for confirmation of the finding. Reassessments of non-qualifying screening labs must be reviewed and approved by the Medical Monitor prior to obtaining the new specimen. The clinical rationale for performing repeat testing of screening assessments should be thoroughly documented.

Standard clinical laboratory evaluations for safety chemistry, coagulation, and hematology will be conducted at all study visits and the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event). Clinically significant abnormal creatinine results at Week 12 (or the ET Visit, if applicable) will also be followed-up 2 weeks (±3 days) after the last dose of study drug in addition to the 4 week (±3 days) Follow-up Visit. See Appendix B for a list of clinical laboratory analytes.

A full fasting lipid panel will be assessed at the Pre-Screening Visit, if applicable, and at all other study visits, including the Follow-up Visit. Fasting apolipoproteins and LDL-C (ultracentrifugation) will be assessed at Study Day 1, Week 10, Week 12, the Follow-Up Visit, and the ET Visit, if applicable. In addition to these lipid parameters, hsCRP, IL-6, SAA, and fibrinogen will also be measured at Study Day 1, Week 10, Week 12, and the ET Visit, if applicable. Finally, ANGPLT4, adiponectin and cystatin-C will be measured at Study Day 1 and Week 12 (or the ET Visit, if applicable).

A urine sample for urinalysis will be collected at the Pre-Screening Visit, if applicable, the Screening Visit, Study Day 1, Week 6, Week 12, the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event), and the ET Visit, if applicable. Urine protein:creatinine ratio and albumin:creatinine ratio will be performed at the Screening Visit, Study Day 1, Week 6, Week

12, the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event), and the ET Visit, if applicable. Urinary NGAL will be measured at Study Day 1, Week 6, Week 12, the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event).

Tests for HBV, HCV, and HIV will be conducted at the subject's first study visit, either at the Pre-Screening Visit, if applicable, or the Screening Visit.

For women of child-bearing potential only, a serum pregnancy test will be conducted at the Screening Visit, Week 12, and the ET Visit, if applicable. A urine pregnancy test will be conducted at the Pre-Screening Visit, Study Day 1, Week 2, Week 6, and Week 10.

Thyroid-stimulating hormone will be measured at the subject's first study visit, either at the Pre-Screening Visit, if applicable, or the Screening Visit.

Fasting insulin levels and FPG will be measured at Study Day 1 and Week 12.

HbA1c will be measured at the subject's first study visit, either at the Pre-Screening Visit, if applicable, or the Screening Visit, Study Day 1 and Week 12.

The estimated blood volume for the full study is 625 mL.

8.7 Vital Signs

Measurement of vital signs will include an assessment of pulse rate, blood pressure, respiration rate, and temperature. Vital signs will be measured at all study visits, excluding the Follow-up Visit. Blood pressure should be obtained in the seated position, after the subject 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 diastolic 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 subject throughout the study when possible. Care should be taken to ensure an appropriate cuff size is utilized.

8.8 Electrocardiograms

Electrocardiograms (ECGs) will be performed in triplicate and sent to a central reviewer. Subjects 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 at the Screening Visit, Study Day 1, Week 2, Week 6, Week 10, Week 12, and the ET Visit, if applicable.

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/SAE as applicable. All ECG traces will be kept as source data.

8.9 Physical Examinations

A full physical examination will be performed at the subject's first study visit, either at the Pre-Screening Visit, if applicable, or the Screening Visit, Week 12, and the ET Visit, if

applicable. 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 the Screening Visit (only for subjects who required a Wash-Out Period and completed the full physical examination at the Pre-Screening Visit), Study Day 1, Week 2, Week 6, Week 10 and the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event).

Height will be measured at the subject's first study visit, either at the Pre-Screening Visit, if applicable, or the Screening Visit and weight will be measured at all study visits, excluding the Follow-up Visit. BMI will be calculated at the Pre-Screening Visit or Screening Visit, Day 1, Week 10, and Week 12. Waist circumference will be measured at Day 1 and Week 12 [or the ET Visit, if applicable].

8.10 Medical/Surgical History and Demographics

Medical and surgical history and demographics will be recorded at the Pre-Screening Visit, if applicable, and/or the Screening Visit. Subject eligibility will be evaluated to determine all inclusion and none of the exclusion criteria are met. The Investigator will inquire with the subject at Study Day 1 to determine if there have been any changes in the subject's health affecting eligibility or requiring an update to their medical and surgical history.

8.11 Reserve Samples and Pharmacokinetics (PK)

Additional blood samples will be collected at all study visits during the Treatment Period and the ET Visit, if applicable, to be available for analysis of exploratory biomarkers associated with lipid metabolism (which may include but will not limited to RLP-C, RLP-TG and RLP-apoB, Lp(a), ox-LDL, and Lp-PLA2), repeat lipid testing, blood drug levels including use in confirming subject compliance (PK analysis), and/or repeat or additional clinical laboratory testing in the event of a safety issue.

Reserve samples will be stored for a minimum of 1 year following study completion and may be stored until the IND is withdrawn or the NDA is approved. If requested, results of tests performed on study samples will be made available to subjects or investigators. Subjects may not withdraw their samples.

The plasma reserve samples collected at Week 2, Week 6, Week 10 and Week 12 [or the ET Visit, if applicable] will be used for the analysis of PK. To facilitate the analysis of PK samples, the time and date of the last dose of study medication and statin if applicable (generic name and strength) prior to the clinic visit will be collected by the subject via a diary. In addition, the time and date of the PK blood sample at the clinic visit will be collected.

8.12 Diary

All subjects will complete a Sponsor-provided paper diary prior to all study visits that require PK samples. The subject will document the exact date and time of their last dose of study drug and,

if applicable, the last date and time of statin dosing. All diaries should be confirmed to be complete by the Principal Investigator or designee and maintained in the subject's records.

9 STATISTICS

9.1 Sample Size

Approximately 90 subjects (30 subjects per treatment group) will be randomized into 1 of 3 treatment groups: gemcabene 300 mg, gemcabene 600 mg or placebo.

A sample size of 30 randomized subjects in the gemcabene 300 mg group, 30 randomized subjects in the 600 mg group and 30 randomized subjects in the placebo group is expected to provide 80% power to detect a difference of 35% in the percent change in TG from baseline to end of study (EOS) between either of the gemcabene treatment groups and the placebo group. This calculation is based on a 2-sided t-test at the 5% level of significance ($\alpha = 0.05$), a common standard deviation of 43, and a drop-out rate of 15%.

9.2 Analysis Populations

9.2.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who receive at least 1 dose of study drug and have at least 1 post-baseline efficacy assessment. The FAS population will be the primary analysis population. All efficacy analyses will be performed on the FAS.

9.2.2 Per Protocol Set

The Per Protocol Set (PPS) will include all FAS subjects who complete the 12-week Treatment Period without major protocol deviations. The PPS will be used to assess robustness of the analysis results. Protocol deviations will be reviewed and the PPS will be determined prior to database lock.

9.2.3 Safety Analysis Set

The Safety Analysis Set (SAS) will include all randomized subjects who receive at least 1 dose of study drug. All safety analyses will be conducted on SAS.

9.3 Statistical Methods

9.3.1 Analysis of Efficacy

9.3.1.1 Primary efficacy analyses

The primary efficacy endpoint is the percent change in fasting serum TG from baseline to EOS. Baseline will be defined as the average of the (Screening Visits [S1 and S2] or [S2 and S3] occurring up to 28 days prior to Study Day 1) and Study Day 1 [pre-dose]) values. EOS will be defined as the average of Week 10 and Week 12. If either the Week 10 or Week 12 value is missing, then the single value (Week 10 or Week 12) will be used. Completely missing values (both Week 10 and Week 12) will be imputed using last observation carried forward (LOCF), with the last on-treatment value carried forward as the EOS value.

The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA) with percent change from baseline to EOS in TG as the dependent variable; treatment and baseline statin (yes or no) as factors; and baseline fasting serum TG as a covariate. The ANCOVA will be performed using the FAS, with subjects included in their randomized treatment group regardless of the treatment they actually received. The least-squares mean (LSM) and standard error (SE) will be provided for each treatment group, along with the placebo-corrected LSM, its 95% confidence interval (CI), and associated p value for both gemcabene groups. A 2-sided test with a significance level of 0.05 will be used for the comparison of the gemcabene 300 mg and 600 mg groups separately to the placebo group. If non-normality is detected, then either the data will be transformed so that it is normally distributed or a nonparametric test will be used.

A confirmatory analysis of the primary efficacy endpoint will be performed using the PPS.

9.3.1.2 Secondary efficacy analyses

Secondary efficacy endpoints include:

- Change and percent change from baseline to Weeks 2, 6, 10 and 12 in fasting serum TG, and change from baseline to EOS in fasting serum TG;
- Change and percent change from baseline to Weeks 2, 6, 10, 12 and EOS in total cholesterol (TC), non-HDL-C, HDL-C, and VLDL-C;
- Change and percent change from baseline to Weeks 10, 12 and EOS in Apo B, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, and ApoE;
- Change and percent change from baseline to Weeks 10, 12 and EOS in LDL-C (ultracentrifugation), LDL-TG, VLDL-TG, HDL-TG;
- Change and percent change from baseline to Week 12 in lipoprotein size and particle number (NMR);
- Change and percent change from baseline to Week 12 in hsCRP, IL-6, SAA, ANGPTL4, adiponectin and fibrinogen; and
- Percent of subjects achieving a TG value <500 mg/dL (5.65 mmol/L) at EOS.

For continuous secondary efficacy endpoints, the same ANCOVA model outlined above for the primary efficacy endpoint will be used, with the respective baseline included as the covariate. Baseline for TC, non-HDL-C, HDL-C, and VLDL-C will be defined as the average of the last two pre-dose values (generally will be the average of Visit S2 and pre-dose Study Day 1/Visit T1). Baseline for fasting apolipoproteins, LDL-C (ultracentrifugation), LDL-TG, VLDL-TG, HDL-TG, hsCRP, IL-6, SAA, adiponectin, fibrinogen, and ANGPTL4 is defined as the value from pre-dose Study Day 1/Visit T1. For the EOS time point, EOS will be defined as the average of Week 10 and Week 12. If either the Week 10 or Week 12 value is missing, then the single value (Week 10 or Week 12) will be used. Completely missing values (both Week 10 and Week 12) will be imputed using LOCF, with the last on-treatment value carried forward as the EOS value. For all other time points, missing values will be imputed using LOCF, with the last on-treatment value carried forward to that time point.

Each ANCOVA will be performed using the FAS, with subjects included in their randomized treatment group regardless of the treatment they actually received. The output from each ANCOVA will include the LSM and SE for each treatment group, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value for both gemcabene groups. For every continuous endpoint (each parameter, each time point), if non-normality is detected, then either the data will be transformed so that it is normally distributed or a nonparametric test will be used.

The percent of subjects achieving a TG value <500 mg/dL (5.65 mmol/L) will be analyzed using a logistic regression with treatment, baseline statin use (yes or no) and baseline TG value as independent factors. The percent of subjects in each treatment group achieving a TG value <500 mg/dL, and the odds ratios with 95% confidence intervals and p-values will be presented to compare gemcabene 300 mg and gemcabene 600 mg separately with the placebo group.

The secondary efficacy analyses will be repeated using the PPS.

9.3.1.3 Exploratory analysis

The exploratory efficacy endpoints include:

- CI [redacted]

For each continuous exploratory endpoint, an ANCOVA will be performed, with the relevant baseline as the covariate. In general, baseline and EOS will be defined as described above in the primary and secondary efficacy analysis sections. Baseline for fasting insulin levels, FPG and HbA1c is defined as the value from pre-dose Study Day 1/Visit T1. The FAS will be used for each analysis, with subjects included in their randomized treatment group regardless of the treatment they actually received. For the analysis of fasting insulin levels, FPG and HbA1c, the FAS that includes only subjects with diabetes at baseline will be used. Where appropriate, relevant subgroups will be used (e.g., within each TG stratum). For each endpoint, the LSM and SE for each treatment group will be provided, along with the placebo-adjusted LSM, 95% CI and p-value for both gemcabene groups.

The percent of diabetic subjects with >5% decrease in dosage of anti-diabetes pharmacologic treatment from baseline to Week 12 will be analyzed using logistic regression with treatment, baseline statin use (yes or no) and baseline TG value as independent factors. The percent of diabetic subjects in each treatment group with > 5% decrease, and the odds ratios with 95%

confidence intervals and p-values will be presented to compare gemcabene 300 mg and 600 mg separately with the placebo group.

The exploratory efficacy analyses will be repeated using the PPS.

9.3.2 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. In addition, the safety assessment will be based primarily on the frequency of new or worsening adverse events, laboratory abnormalities, and serious adverse events (SAEs). Other safety data will be summarized as appropriate.

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). The summarization of AEs will include only treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

Safety laboratory data will be summarized by treatment group at baseline, and at each post-baseline time point, if applicable, and change from baseline to End of Treatment (Week 12) or the ET Visit, if applicable. Baseline for safety laboratory data will be defined as the last pre-dose value (pre-dose Study Day 1/Visit T1 or prior). Frequency counts of new or worsening abnormalities will also be provided.

Vital signs data (value and change from baseline, where appropriate) will be summarized by treatment group at baseline and at each post-baseline time point. Baseline for vital signs data will be defined as the last pre-dose value (pre-dose Study Day 1/Visit T1 or prior). Abnormalities in ECGs and in PEs will be summarized.

All safety data will be listed.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be collected and processed using a validated EDC system. The system and procedures are designed in compliance with Title 21 of the Code of Federal Regulations (21 CFR Part 11).

10.1.3 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. These procedures must comply with 21 CFR Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

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

10.1.5 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 the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor 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 Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 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 subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 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 subjects in research studies. The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. 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 subjects, 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 subject recruitment, and any other written information regarding this study being provided to a subject or subject'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.

11.3 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 subject (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 subject has been informed of his/her rights to privacy. The Investigator or delegate will allow the subject adequate opportunity to read the written informed consent and ask any questions. The Investigator will obtain written informed consent from each subject 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 subject 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 subject.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki (Seoul 2008) and that valid data are entered into the eCRFs.

The role of the study monitor is to verify the rights and well-being of the subjects are protected, the data is accurate, complete, and verifiable from source documents, and the conduct of the study is in compliance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, management of investigational product, and the procedure for reporting adverse events such as SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log and findings documented in a follow-up letter.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/EC as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

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

11.6 Retention of Records

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., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, 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, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 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. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves 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.

11.8 Financial Disclosure

Clinical Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR §54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.9 Insurance and Indemnity

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

11.10 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

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

11.11 Definition of End of Study

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

11.12 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 Gemphire. In addition, Gemphire retains the right to discontinue development of gemcabene at any time.

If a study is prematurely terminated or discontinued, Gemphire will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects within 2 weeks. As directed by Gemphire, all study materials must be collected and all eCRFs completed to the greatest extent possible.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by PI or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented only after it has been approved by the IRB/REB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

12.2 Address List

12.2.1 Sponsor

Gemphire Therapeutics Inc.
17199 N. Laurel Park Drive, Suite 401
Livonia, MI 48152
Telephone: +1-248-681-9815
Facsimile: +1-734-864-5765

12.2.2 Contract Research Organization

PI

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APPENDIX A: SCHEDULE OF PROCEDURES

	Pre-Screening[a]	Screening[b,f]				Treatment Period[c]				Follow-Up[d]	ET
		Study Day -28 to -21	Study Day -14 to -7	Study Day-7	Study Day 1[e]	Week 2/ Study Day 15±3 days	Week 6/ Study Day 43±3 days	Week l0/ Study Day 71±3 days	Week 12/ Study Day 85 or up to 3 days prior to Study Day 85	Study Day 113	
	Visit Identifier	Visit S1	Visit S2	Visit S3	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5	Visit FU1	
Informed consent	X	X									
Inclusion/exclusion criteria	X	X	X	X	X						
Medical/surgical history and demographics	X	X	X	X	X						
Full physical examination[g]	X	X							X		X
Symptom-directed physical examination		X[h]			X	X	X	X		X[i]	
Vital signs[j], height[k], and weight	X	X	X	X	X	X	X	X	X		X
Body Mass Index (BMI)	X	X			X			X	X		X
Waist circumference					X				X		X
Urinalysis + NAGL[l]	X	X			X		X		X	X[i]	X
Protein:creatinine ratio; albumin:creatinine ratio	X	X			X		X		X	X[i]	X
Serum/urine pregnancy test[m]	X	X			X	X	X	X	X	X[i]	X
Safety chemistry panel, coagulation, and hematology[n]	X	X	X	X	X	X	X	X	X	X[i]	X
TSH and serology[o]	X	X[f]									
Fasting lipid panel[p]	X[q]	X	X	X	X	X	X	X	X	X	X
Fasting apolipoproteins[r]					X			X	X	X	X
LDL-C ultracentrifugation (LDL-C, LDL-TG, VLDL-TG)					X			X	X	X	X
CI [redacted]					X				X		X
HbA1c	X	X			X				X		X
Cystatin-C, ANGPLT4, adiponectin					X				X		X

hsCRP, SAA, IL-6, and fibrinogen					X			X	X		X
Lipoprotein size and particle number					X				X		X
Randomization					X						
Study drug administration[s]					X	X	X	X			
Dispense study drug and instructions					X	X	X	X			
Compliance check						X	X	X	X		X
Distribute drug diary					X	X	X	X			
Dietary assessment (self-reported)[t]	X	X	X	X	X	X	X	X			
12-lead ECG[u]		X			X	X	X	X	X		X
Initiate wash-out	X										
Adverse events	X[v]	X[v]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X[f]	X	X	X	X	X	X	X	X	X
Reserve serum samples[w]					X	X	X	X	X		X
Reserve plasma PK samples[x]					X	X	X	X	X		X
Collect drug diary						X	X	X	X		X
Reserve genotyping sample					X						

Footnotes appear on the following page

a. Only subjects requiring a Wash-Out Period will participate in the Pre-Screening Visit. Specifically, PCSK9 inhibitors will require an 8-week Wash-Out Period, fibrates will require a 6-week Wash-Out Period, and niacins, OMG-3, bile acid sequestrants or other lipid-regulating therapies will require a 4-week Wash-Out Period, prior to the Screening Visit.
b. All eligible subjects will participate in the Screening Visit up to 28 days prior to Study Day 1. For subjects taking the required stable statin therapy for >12 weeks at the Screening Visit and do not require a Wash-Out Period, the Screening Visit will be their first study visit.
c. Study assessments will be completed ±3 days of given time point for all study visits from Study Day 1 through Week 10. Week 12 assessments can be performed up to 3 days prior to Study Day 85, but not after Study Day 85.
d. The Follow-up Visit will be conducted as a telephone call 4 weeks (±3 days) after the last dose of study drug, unless the subject requires a site visit due to an abnormal result at Week 12 (or the ET Visit, if applicable) or an ongoing treatment-related adverse event.
e. Procedures will be performed pre-dose. The Investigator will inquire with the subject at Study Day 1 to determine if there have been any changes in the subject's health affecting eligibility or requiring an update to their medical and surgical history.
f. For subjects 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, HbA1c, and serology (HBV, HCV, and HIV) screening. Updates, as needed, will be made to medical/surgical history, demographics, and concomitant medications.
g. A full physical examination includes genitourinary examination per the Investigator's discretion and does not include a rectal examination.
h. Only for subjects who required a Wash-Out Period and completed the full physical examination at the Pre-Screening Visit.
i. Only for subjects who had an abnormal result at Week 12 (or the ET Visit, if applicable) or an ongoing treatment-related adverse event.
j. Vital signs include pulse rate, blood pressure, respiration rate, and temperature. Blood pressure should be obtained in the seated position, after the subject 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. If an automated assessment is performed, the same machine should be used for the subject throughout the study when possible. Care should be taken to ensure an appropriate cuff size is utilized.
k. Height will be measured only at the subject's first study visit, either at the Pre-Screening Visit or the Screening Visit.
l. Urine will be collected for a full urinalysis at the lab including protein:creatinine ratio and albumin:creatinine ratio at the Prescreening/screening Visit, Study Day 1, Week 6, Week 12, the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event), and the ET Visit, if applicable. Urinary NGAL will be measured at Study Day 1, Week 6, Week12, the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event), and the ET Visit, if applicable.
m. For women of child-bearing potential only, a serum pregnancy test will be conducted at the Screening Visit, Week 12, and the ET Visit, if applicable. A urine pregnancy test will be conducted at the Pre-Screening Visit, Study Day 1, Week 2, Week 6, and Week 10.
n. Clinically significant abnormal creatinine results at Week 12 (or the ET Visit, if applicable) will also be followed-up 2 weeks (±3 days) after the last dose of study drug in addition to the 4 week (±3 days) Follow-up Visit. See Appendix B for a list of analytes and description of when repeat or reflexive testing will be required.
o. Thyroid-stimulating hormone, HbA1c, and serology (HBV, HCV, and HIV) will be measured at the subject's first study visit, either at the Pre-Screening Visit, if applicable, or the Screening Visit.
p. Includes non-HDL-C, TC, TG, HDL-C, and VLDL-C and HDL-TG. Fasting will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Subjects will be permitted to have water, black tea or black coffee.
q. Includes TG only. Fasting will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Subjects will be permitted to have water, black tea or black coffee.
r. Includes ApoB, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, and ApoE. Fasting will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Subjects will be permitted to have water.
s. Study drug will be administered at the site on Study Day 1. Subjects will self-dose at all other times during the Treatment Period.
t. Subjects will self-report compliance to a stable, heart-healthy diet.
u. Subjects should be lying quietly in a fully supine position for at least 10 minutes prior to each 12-lead ECG.

v. 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 eCRF.
w. The following may be analyzed: RLP-C, RLP-TG and RLP-apoB, Lp(a), ox-LDL, and Lp-PLA2.
x. Plasma samples collected at Week 2, Week 6, Week 10, Week 12 and ET will be used for the analysis of gemcabene PK. The plasma sample collected at Day 1 will be reserve.

Apo = apolipoprotein; ECG = electrocardiogram; eCRF = electronic case report form; ET = Early Termination; HBV = hepatitis B virus; HbA1c = hemoglobin A1c; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; HoFH = homozygous familial hypercholesterolemia; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); NCEP ATP-III = National Cholesterol Education Program Adult Treatment Panel III; NGAL = neutrophil gelatinase-associated lipocalin; non-HDL-C = non-high-density lipoprotein cholesterol; 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.
3. For an estimated GFR decrease of >15 mL/min from baseline during the study, repeat chemistry will be performed.

Additional Chemistry Parameters

Cystatin-C
Fasting plasma glucose
HbA1c
Fasting insulin

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	Neutrophil gelatinase-associated lipocalin
Albumin	(NGAL) [3]

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 Screening Visit, Study Day 1, Study Day 28, Study Day 85, the Follow-up Visit (only for subjects who had an abnormal result at Study Day 85 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event), and the ET Visit, if applicable.
3. Urine protein:creatinine ratio will be performed at the Screening Visit, Study Day 1, Study Day 28, Study Day 85, the Follow-up Visit (only for subjects who had an abnormal result at Study Day 85 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event), and the ET Visit, if applicable.
4. Urinary NGAL will be measured at Study Day 1, Study Day 28, Study Day 85, the Follow-up Visit (only for subjects who had an abnormal result at Study Day 85 [or the ET Visit, if applicable] 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 subjects 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
ANGPTL4	Fibrinogen

APPENDIX C: NEW YORK HEART ASSOCIATION CONGESTIVE HEART FAILURE CLASSIFICATION

- Class I: subjects 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: subjects 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: subjects 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: subjects 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: REFERENCE LIST OF CYTOCHROME P450 3A4 INHIBITOR EXCLUSIONARY MEDICATIONS

Amiodarone
Amprenavir
Atazanavir
Cimetidine
Clarithromycin
Conivaptan
Darunavir
Delavirdine
Diltiazem
Erythromycin
Fluconazole
Fluvoxamine
Fosamprenavir
Grapefruit juice
Imatinib
Indinavir
Itraconazole
Ketoconazole
Lopinavir
Miconazole
Mibefradil
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telithromycin
Tipranavir
Troleandomycin
Verapamil
Voriconazole

APPENDIX E: MUSCLE INJURY AND HEPATIC MONITORING

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

- Subjects 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.
- Subjects 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 subjects with CK elevations >10 × ULN should have an unscheduled visit (+ isozymes). Study drug should be temporarily discontinued, pending the results of an investigation into the cause of muscle injury and/or CK elevation is complete.

It is important that subjects 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 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 alanine aminotransferase (ALT) >2 × ULN with symptoms suggestive of hepatitis should have an unscheduled visit. Subjects with ALT >3 × ULN with or without symptoms should also have an unscheduled visit. A repeat assessment should be performed as soon as possible 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.

Study drug should be temporarily discontinued during this evaluation if the subject has signs or symptoms of hepatitis or an ALT >5 × ULN. 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.

<u>Recommended Hepatic Discontinuation Criteria</u>

Study drug should be discontinued permanently if 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. Abnormal values should be 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.