Title: A 12-Week, Phase 2 Randomized, Placebo-Controlled, Double-Blind Study to Assess the Efficacy, Safety, and Tolerability of Gemcabene in Subjects with Hypercholesterolemia Not Adequately Controlled on High-Intensity or Moderate-Intensity Stable Statin Therapy (ROYAL-1)

NCT ID: NCT02634151

Approval Date: 05-Oct-2016

CLINICAL STUDY PROTOCOL

A 12-Week, Phase 2 Randomized, Placebo-Controlled, Double-Blind Study to Assess the Efficacy, Safety, and Tolerability of Gemcabene in Subjects with Hypercholesterolemia Not Adequately Controlled on High-Intensity or Moderate-Intensity Stable Statin Therapy (ROYAL-1)

Investigational Product: Gemcabene calcium tablets (gemcabene)
Protocol Number: GEM-301

Sponsor:
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Original Protocol: 25 November 2015
Amendment 1: 19 February 2016
Amendment 2: 16 September 2016
Amendment 3: 05 October 2016

SIGNATURE PAGE

STUDY TITLE: A 12-Week, Phase 2 Randomized, Placebo-Controlled, Double-Blind Study to Assess the Efficacy, Safety, and Tolerability of Gemcabene in Subjects with Hypercholesterolemia Not Adequately Controlled on High-Intensity or Moderate-Intensity Stable Statin Therapy (ROYAL-1)

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

Signature Date

PI

10/5/16

Gemphire Therapeutics Inc.

PI

10/5/16

Gemphire Therapeutics Inc.

PI

10/5/16

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: A12-Week, Phase 2 Randomized, Placebo-Controlled, Double-Blind Study to Assess the Efficacy, Safety, and Tolerability of Gemcabene in Subjects with Hypercholesterolemia Not Adequately Controlled on High-Intensity or Moderate-Intensity Stable Statin Therapy (ROYAL-1)

PROTOCOL NUMBER: GEM-301

INVESTIGATIONAL PRODUCT: Gemcabene calcium tablets (gemcabene)

PHASE: 2

INDICATION(S): For the treatment of hypercholesterolemia, including subjects with heterozygous familial hypercholesterolemia (HeFH) and subjects with atherosclerotic cardiovascular disease (ASCVD), not adequately controlled on stable statin therapy.

OBJECTIVES:

The primary objective of this study is to assess the LDL-C lowering of gemcabene 600 mg once daily (QD) compared to placebo in subjects with hypercholesterolemia not adequately controlled on high-intensity or moderate-intensity stable statin therapy treated for 12 weeks.

The secondary objectives of this study are the following:

- To assess the LDL-C lowering of gemcabene 600 mg in (1) subjects on high-intensity statin therapy; and (2) subjects on moderate-intensity stable statin therapy treated for 12 weeks.
- To assess the safety and tolerability of gemcabene 600 mg in all subjects combined and separately in (1) subjects on high-intensity statin therapy; and (2) subjects on moderate-intensity stable statin therapy treated for 12 weeks.
- To assess the effect of gemcabene on other lipid and apolipoprotein parameters, high-sensitivity C-reactive protein (hsCRP), serum amyloid A (SAA), adiponectin, fibrinogen, and cardiovascular risk after 12 weeks of treatment.

The exploratory objectives of this study are the following:

- CI [redacted]

POPULATION:

The population for this study is male and female subjects, ≥18 years of age with or without diabetes. Subjects must have a fasting LDL-C value ≥100 mg/dL (2.59 mmol/L) and a TG value

< 500 mg/dL (5.65 mmol/L) at the Screening Visit, while on a stable, low-fat, low-cholesterol diet in combination with background high-intensity statin therapy (defined as atorvastatin 40 mg or 80 mg once daily [QD]; or rosuvastatin 20 mg or 40 mg QD) or background moderate-intensity statin therapy (defined as atorvastatin 10 mg or 20 mg QD; or rosuvastatin 5 mg or 10 mg QD; or simvastatin 20 or 40 mg QD) with or without ezetimibe 10 mg QD for at least 12 weeks prior to the Screening Visit.

STUDY DESIGN AND DURATION:

This is a Phase 2, randomized, placebo-controlled, double-blind, multi-center study. Subjects are required to be on a high-intensity stable statin regimen (atorvastatin 40 mg or 80 mg QD or rosuvastatin 20 mg or 40 mg QD) or a moderate-intensity statin regimen (atorvastatin 10 mg or 20 mg QD; rosuvastatin 5 mg or 10 mg QD; or simvastatin 20 or 40 mg QD) with or without ezetimibe 10 mg for at least 12 weeks prior to the Screening Visit.

Approximately 104 subjects will be randomized into the study, including those with HeFH or ASCVD, with 52 (26 gemcabene 600 mg; 26 placebo) subjects on baseline high-intensity statins and 52 (26 gemcabene 600 mg; 26 placebo) subjects on baseline moderate-intensity statins. 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), a Screening Visit, a Treatment Period, and a Follow-up Visit.

A wash-out period will be required for eligible subjects taking any lipid-regulating therapies or supplements, with the exception of atorvastatin 10 mg, 20 mg, 40 mg and 80 mg QD; rosuvastatin 5 mg, 10 mg, 20 mg and 40 mg QD; simvastatin 20 mg and 40 mg QD; and ezetimibe 10 mg QD. 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. 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 niacins or other lipid-regulating therapies such as bile acid sequestrants will require a 4-week wash-out period prior to the Screening Visit.

All eligible subjects will participate in the Screening Visit up to 14 days prior to Day 1. For eligible subjects taking the required moderate or high-intensity stable statin therapy for ≥ 12 weeks and who do not require a wash-out period, the Screening Visit will be their first study visit.

The duration of the Treatment Period will be 12 weeks. Eligible subjects will be randomized via an interactive web/voice response system (IWRS/IVRS) on Day 1 in a 1:1 ratio to the following treatment groups: placebo or gemcabene 600 mg. Subjects will be stratified by statin intensity (high-intensity or moderate-intensity as defined in Table 1) and diabetes (yes or no). Subjects defined as diabetic will be those receiving concomitant anti-diabetic medication at screening. Randomization within a baseline statin intensity stratum will be capped at 52 subjects; once 52 subjects are randomized into a baseline statin intensity stratum, no further subjects in that statin intensity stratum will be randomized (subjects in the other baseline statin intensity stratum will continue to be randomized until there are 52 randomized subjects in that stratum). By also stratifying on diabetes status (yes, no) at baseline, diabetic subjects will be evenly distributed across the treatment groups and statin-intensity subgroups. The first dose of study drug will be

administered at the site on Day 1.

Post-randomization clinic visits will occur at Week 2, Week 4, Week 8 and Week 12. The Follow-up Visit will occur 4 weeks (±3 days) after the last dose of study drug.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Study drug will be prepared as 7-day blister packages with each day's segment containing 3 tablets based on the treatment group:

- 600 mg: two 300 mg gemcabene tablets and 1 placebo tablet, and
- Placebo: 3 placebo tablets.

On days with a scheduled office visit with blood sample collection, subject will remain fasted (at least 10 hours) and should not take gemcabene until after the blood samples are collected. For days when the subject will self-dose, the subject will be instructed to take study drug at the same time in the morning with a full glass (8 ounces) of water either with or without food.

STATISTICAL ANALYSIS:

Sample Size

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C, with the primary focus on the overall set of randomized subjects. The efficacy within each baseline statin intensity (high-intensity; moderate-intensity) stratum is also of interest for this study; thus, the study is powered for the analyses within each baseline statin intensity stratum. A sample size of 26 randomized subjects in the gemcabene 600 mg group and 26 randomized subjects in the placebo group within each baseline statin intensity stratum is expected to provide 80% power to detect a difference of 17% in the percent change from baseline to Week 12 in LDL-C between the gemcabene treatment group and the placebo group within each baseline statin intensity stratum. This calculation is based on a 2-sided t-test at the 5% level of significance ($\alpha = 0.05$), a common standard deviation of 20, and a drop-out rate of 10%. The sample size of 26 randomized subjects in each baseline statin intensity stratum in the gemcabene 600 mg group gives a total of 52 randomized subjects in the gemcabene 600 mg group. Twenty-six randomized subjects in each baseline statin intensity stratum in the placebo group gives a total of 52 randomized subjects in the placebo group. Thus, the total study sample size is 104 randomized subjects.

There are no planned interim analyses for this study.

Subject Population

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. All efficacy analyses will be performed on the FAS.

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 the SAS.

EFFICACY ENDPOINTS AND ANALYSIS

The primary efficacy endpoint will be compared to a significance level of 0.05. Each of the secondary and exploratory efficacy endpoints will also be compared to a significance level of 0.05. That is, analysis of secondary and exploratory endpoints will not be adjusted for multiplicity. Given the large number of secondary and exploratory endpoints, p-values for these endpoints will be considered descriptive.

Primary

The primary efficacy endpoint is the percent change from baseline to Week 12 in fasting LDL-C. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA) with percent change from baseline to Week 12 in LDL-C as the dependent variable; treatment, baseline statin intensity (high-intensity; moderate-intensity), and baseline diabetes (yes or no) as factors; and baseline fasting LDL-C as a covariate. Baseline will be defined as the average of the LDL-C values at Screening/Visit S1 and pre-dose Day 1/Visit T1. The ANCOVA will be performed using the FAS, with subjects included in their randomized treatment group regardless of the treatment they actually received. Missing values for Week 12 will be imputed using last observation carried forward (LOCF); only post-baseline values will be used for the imputation. The least-squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI), and associated p-value. A 2-sided test with a significance level of 0.05 will be used for the comparison of gemcabene 600 mg 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

Secondary efficacy endpoints include

- Percent change from baseline to Week 12 in LDL-C within each statin intensity stratum (high-intensity; moderate-intensity);
- Change from baseline to Week 2, Week 4, Week 8, and Week 12 in LDL-C;
- Change and percent change from baseline to the average of Week 8 and Week 12 measurements in LDL-C;
- Change and percent change from baseline to Week 12 in LDL-C in subjects on and not on ezetimibe;
- Change and percent change from baseline to Week 2, Week 4, Week 8, and Week 12 in non-HDL-C, TC, TG, HDL-C and VLDL-C;
- Percent of subjects achieving LDL-C reduction of ≥ 10%, ≥ 15%, and ≥ 20% at Week 4, Week 8, and Week 12;
- Percent of subjects achieving an LDL-C value < 100 mg/dL (2.59 mmol/L) at Week 4, Week 8, and Week 12;
- Change and percent change from baseline to Week 4, Week 8 and Week 12 in ApoB, ApoA-

I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, ApoE and Lp(a);

- Change and percent change from baseline to Week 12 in hsCRP, SAA, adiponectin and fibrinogen;
- Change from baseline to Week 12 in Framingham Risk score; and
- Change from baseline to Week 12 in NCEP ATP-III Risk.

Exploratory

Exploratory efficacy endpoints include:

[redacted]

For continuous secondary and exploratory efficacy endpoints related to change/percent change in basic fasting lipids, lipoproteins, hsCRP, SAA, adiponectin, fibrinogen and [redacted] the same ANCOVA for the primary efficacy endpoint will be used, with the respective baseline included as the covariate. Note that for secondary endpoints such as change from baseline in LDL-C within the moderate-intensity stratum, the ANCOVA model will not include a term for baseline statin intensity stratum. Baseline for TC, non-HDL-C, HDL-C and VLDL-C are defined similarly to baseline for LDL-C. Baseline for fasting lipoproteins, insulin and plasma glucose; hsCRP, SAA, adiponectin, fibrinogen, and serum [redacted] are defined as the value from pre-dose Day 1/Visit T1. Baseline for HbA1c is the value from the first visit (Pre-Screening or Screening Visit).

Each ANCOVA will be performed using the FAS (or the specific subgroup within the FAS that is indicated in the specific endpoint [e.g. subgroup of baseline high-intensity statin subjects]), with subjects included in their randomized treatment group regardless of the treatment they actually received. Missing values for post-randomization time points will be imputed using last observation carried forward (LOCF); only post-baseline values will be used for the imputation. The output from each ANCOVA will include the LSM and SE for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value. 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 LDL-C reduction of ≥10%, ≥15% and ≥ 20% at Week 4, Week 8, and Week 12 will each be analyzed using a logistic regression with treatment, baseline statin intensity (high-intensity; moderate-intensity), baseline diabetes (Y/N) and baseline LDL-C value as independent factors. For each analysis, the percent of subjects in each treatment group meeting the criteria, the odds ratios with 95% CI, and p-value will be provided. The percent of subjects achieving a LDL-C value <100 mg/dL (2.59 mmol/L) at Week 4, Week 8, and Week 12

will be analyzed in the same manner, with similar output provided for each endpoint. For all of these endpoints, the FAS will be used, with subjects included in their randomized treatment group regardless of the treatment they actually received.

Framingham Risk scores and estimated 10-year risk will be summarized at baseline and Week 12. Additionally, the change from baseline to Week 12 in Framingham Risk scores and estimated 10-year risk will be summarized. The number and percent of subjects in each NCEP ATP-III Risk category will be summarized at baseline and Week 12. Also, a shift table of NCEP ATP-III Risk categories from baseline and Week 12 will be provided. The FAS, with subjects included in their randomized treatment group regardless of the treatment they actually received, will be used for all of these summarizations. Finally, the percent of diabetic subjects in the FAS with a reduction in their anti-diabetic medications greater than 5% from baseline to Week 12 will be summarized by treatment group. In addition, change from baseline [or first visit (Pre-Screening or Screening)] to Week 12 in fasting insulin, FPG, and HbA1c in diabetic subjects in the FAS will also be summarized by treatment group.

Confirmatory analysis of the secondary and exploratory endpoints will be performed using the PPS.

SAFETY ENDPOINTS AND ANALYSIS:

The safety variables include adverse events, safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) with particular attention to hepatic (e.g., alanine aminotransferase/aspartate aminotransferase, bilirubin, alkaline phosphatase), renal (e.g., blood urea nitrogen, serum creatinine, protein:creatinine ratio, albumin:creatinine ratio, neutrophil gelatinase-associated lipocalin (NGAL), urinalysis sediments, pH, electrolytes), and skeletal muscle (i.e., creatine kinase) toxicities, 12-lead electrocardiograms (ECGs), physical examinations, and vital signs.

No statistical analysis of safety data will be performed in this study. Safety will be assessed using the SAS with subjects included in the treatment group they actually received, regardless of their randomized treatment. The assessment of safety will include adverse events, clinical laboratory assessments, ECGs, physical examinations, and vital signs. Observed case data will be used.

Adverse events (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 (including indicators of hepatic, renal, muscle, coagulation and hematologic effects) will be summarized by treatment group at baseline and at each post-baseline time point. Change from baseline to each time point, if appropriate, will also be summarized by treatment group. Baseline for safety laboratory data will be defined as the last pre-dose measurement (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 measurement (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 20 sites in the United States.

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance model
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
ET	Early Termination
FAS	Full analysis set
FDA	Food and Drug Administration
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
HoFH	Homozygous familial hypercholesterolemia
hsCRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IWRS/IVRS	Interactive web/voice response system
LDL-C	Low-density lipoprotein cholesterol

Lp(a)	Lipoprotein(a)
LSM	Least squares mean
MedDRA	Medical Dictionary for Regulatory Affairs
NCEP ATP-III	National Cholesterol Education Program Adult Treatment Panel III
NGAL	Neutrophil gelatinase-associated lipocalin
NIMP	Non-investigational medical product
non-HDL-C	Non-high-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetics
QD	Once daily
SAA	Serum amyloid A
SAE	Serious adverse event
SE	Standard error
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 is a novel lipid-regulating compound with a dual mechanism of action that involves: (1) blocking the hepatic production of triglyceride (TG) and cholesterol synthesis; and (2) enhancing the clearance of very low-density lipoprotein. Based on prior clinical studies, the combined effects for these mechanisms has been observed to result in a reduction of plasma very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), as well as an elevation in high-density lipoprotein cholesterol (HDL-C). Gemcabene has also been shown to markedly lower high sensitivity C-reactive protein (hsCRP).

Gemphire Therapeutics Inc. (Gemphire) is developing gemcabene as an adjunct to diet and statin therapy for the treatment of subjects with dyslipidemia.

1.2 Dose Selection Rationale

A Phase 1 PK/PD study (1027-003) of gemcabene administered across its dose range (50 mg through 900 mg once daily [QD]) for 2 weeks in healthy volunteers demonstrated clinically and statistically significant dose dependent lowering of LDL-C from 450 mg through 900 mg with a plateau of LDL-C lowering effects observed at 600 mg. Plasma concentration data indicates that gemcabene LDL-C lowering exceeds 25% when AUC (0-24) values are greater than 2500 hr*µg/mL (the range most broadly covered by 600 mg QD) with limited additional LDL-C lowering above 5000 hr*µg/mL. This supported the Sponsor's decision (in the original program conducted over 10 years ago) to test the 600 mg dose and its bordering doses in Phase 2 studies assessing gemcabene's effects in dyslipidemia.

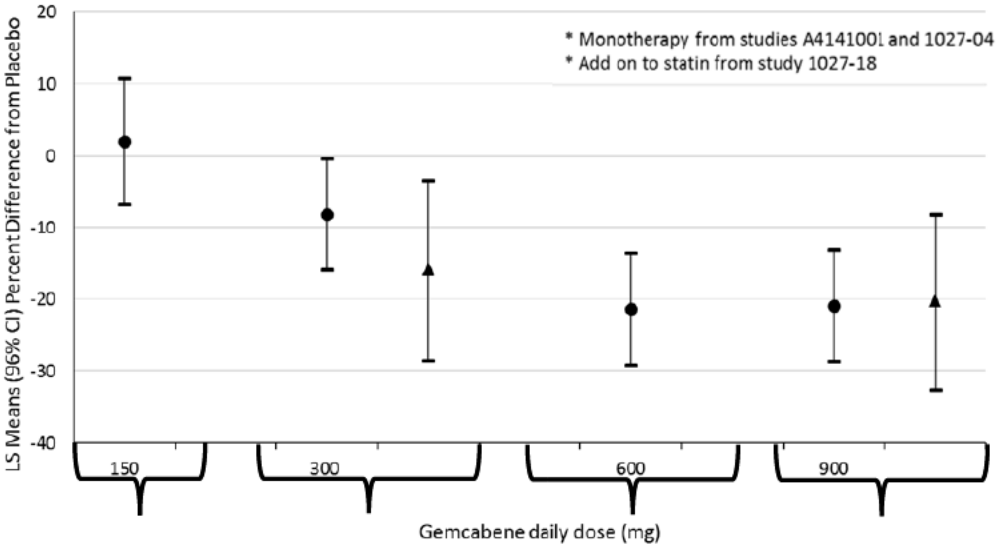
To date, the effect of gemcabene on lipid parameters has been evaluated in three Phase 2 clinical studies involving over 500 subjects with hypercholesterolemia or dyslipidemia. These studies individually demonstrated that the gemcabene LDL-C dose response curve spans the dose range of 150 mg through 900 mg, with a minimum effective dose at 150 mg and a plateau of LDL-C effects at 600 mg (with non-distinguishable additional LDL-C effects at 900 mg compared to 600 mg).

A retrospective integrated analysis of this Phase 2 data was recently performed by Gemphire to determine the LDL-C dose response in subjects with lipid values representative of the subject population included in the gemcabene hypercholesterolemic development program and GEM-301 (LDL-C $\geq$ 100 mg/dL and TG < 500 mg/dL) (n=223).

In an analysis of subjects who received gemcabene *monotherapy* (n=159), including study 1027-004 (low HDL, dyslipidemic subjects) and the monotherapy arm of study 4141001 (hypercholesterolemic subjects), the LDL-C mean % change difference from placebo for gemcabene 150 mg, 300 mg, 600 mg, and 900 mg was +2.0% (p=0.4359), -8.1% (p=0.0001), -21.3% (p<0.0001), and -20.9% (p<0.0001), respectively. The 1027-018 study tested gemcabene 300 mg and 900 mg in hypercholesterolemic subjects on *previously prescribed and stable statin therapy*, a design similar to the current study and the way in which gemcabene is anticipated to be dosed in clinical practice. In this study the LDL-C mean % change difference from placebo for gemcabene 300 mg and 900 mg was -15.9% (p=0.005) and -20.4% (p<0.001), respectively.

Since LDL-C effects were similar across monotherapy and add-on to stable statin therapy (**Figure 1**), the groups were combined in an overall analysis.

Figure 1: Pooled Monotherapy (1025-004; 4141001) and Add-On LDL-C Effects to Stable Statin Therapy (1027-018)



Mean percent change and difference from placebo in LDL-C for gemcabene 150 mg, 300 mg, 600 mg, and 900 mg was +3.6 (p=0.4146), -11.1 (p=0.001); -20.2 (p<0.0001), and -20.9 (p<0.0001), respectively. This was supported by a dose-dependent reduction in atherogenic particles (Apo B) statistically different from placebo at gemcabene 300 mg, 600 mg and 900 mg.

The LDL-C efficacy data outlined above supports the 600 mg dose of gemcabene as the optimal dose for LDL-C lowering to further study in Phase 2 in study GEM-301 prior to testing in Phase 3. GEM-301 is designed to determine additional LDL-C lowering and safety of gemcabene 600 mg over 12 weeks on high-intensity and moderate-intensity stable background statin therapy.

1.3 Risk/Benefit

Statin therapies have been found to consistently and effectively lower LDL-C levels.[1-3] The intensity of prescribed statin therapy is determined based on the expected LDL-C response to a particular statin and dose. The 2013 American College of Cardiology and American Heart Association Task Force guidelines indicate that maximally tolerated, moderate-intensity, and low-intensity statin therapy lower LDL-C by approximately ≥50%, 30% to <50%, and <30%, respectively.[4]

While statins, either as monotherapy or in combination with ezetimibe, are helpful as one line of defense in the treatment of hypercholesterolemia, statins at their maximal dose may not always be well-tolerated by subjects. One common side effect of statin therapy is myalgia, and some clinicians believe that statins may cause myalgia without accompanying creatine kinase (CK) elevations.[5] A review of 2 databases found that myalgia contributed to 19% to 35% and 6% to 14% of all adverse events reported to be associated with use of statins.[5] Further, while statin therapies have been the most effective therapy to lower LDL-C levels, some individuals still fail

to reach target LDL-C levels even with maximally tolerated statin treatment and their risk for cardiovascular disease (CVD) remains elevated.

Other means of treatment, either in combination with statins or as stand-alone therapy, may include cholesterol absorption inhibitors, fibrates, bile acid sequestrants, or newly-approved proprotein convertase subtilkisin/kexin type 9 (PCSK9) inhibitors.

The safety and efficacy profile of gemcabene has been demonstrated through 18 Phase 1 and Phase 2 clinical studies (17 completed and one Phase 1 study stopped due to a business decision), involving 1272 healthy adult subjects and subjects with various dyslipidemias.

The clinical program conducted to date has demonstrated that gemcabene is 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 either as a single dose or as multiple doses QD. This includes 837 subjects who received multiple doses of up to 900 mg for up to 12 weeks. Safety of these subjects was evaluated by adverse event monitoring, clinical laboratory assessments, electrocardiograms (ECGs), physical examinations, and vital sign assessments.

Phase 1 pharmacokinetic (PK) studies have demonstrated that gemcabene is rapidly absorbed following oral administration, with exposure increasing approximately linearly with dose. No clinically meaningful 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 healthy adult subjects 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) decreased slightly 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.

1.4 Rationale

Gemcabene dose response analysis on LDL-C in individual studies as well as across Phase 2 studies indicate gemcabene 600 mg is the optimal dose to move forward for testing in Phase 3. What is not known is the ability of gemcabene at its optimal dose (600 mg) to provide clinically and statistically meaningful LDL-C lowering in subjects not at goal (LDL-C ≥100 mg/dL) while receiving their maximum statin therapy, including high-intensity and moderate-intensity. In the real world clinical setting, high-risk patients are treated with both high-intensity as well as

moderate-intensity statins. Reasons subjects may remain on moderate-intensity statins although not at LDL-C goal include intolerability on high-intensity statins; LDL-C is close to goal at the lower regimen; or perceived intolerance issues, drug interactions and/or safety concerns with high-intensity statins. In order to obtain meaningful data in this small Phase 2 study, subjects on moderate-intensity statins will be included regardless of their reason.

Therefore, the current study will assess the effect of gemcabene 600 mg on LDL-C and other lipids and lipoproteins and hsCRP in subjects with LDL-C $\geq$ 100 mg while on stable statin therapy, of which 50% will be high-intensity and 50% will be moderate-intensity. Efficacy and safety data from this study will be used along with the integrated analysis work from previously completed studies to inform the dose for Phase 3 in subjects with homozygous familial hypercholesterolemia (HoFH), and to confirm gemcabene 600 mg for use in Phase 3 studies in heterozygous FH (HeFH), and atherosclerotic cardiovascular disease (ASCVD).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the LDL-C lowering of gemcabene 600 mg QD compared to placebo in subjects with hypercholesterolemia not adequately controlled on high-intensity or moderate-intensity stable statin therapy treated for 12 weeks.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess the LDL-C lowering of gemcabene 600 mg in (1) subjects on high-intensity statin therapy; and (2) subjects on moderate-intensity stable statin therapy treated for 12 weeks.
- To assess the safety and tolerability of gemcabene 600 mg in all subjects combined and separately in (1) subjects on high-intensity statin therapy; and (2) subjects on moderate-intensity stable statin therapy treated for 12 weeks.
- To assess the effect of gemcabene on other lipid and apolipoprotein parameters, hsCRP, adiponectin, fibrinogen, and cardiovascular risk over 12 weeks of treatment.

2.3 Exploratory Objective

- CI [redacted]

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2, randomized, placebo-controlled, double-blind, multi-center study. Subjects are required to be on either a high-intensity stable statin regimen (atorvastatin 40 mg or 80 mg QD; or rosuvastatin 20 mg or 40 mg QD) or a moderate-intensity statin regimen (atorvastatin 10 mg or 20 mg QD; rosuvastatin 5 mg or 10 mg QD; or simvastatin 20 or 40 mg QD) with or without ezetimibe 10 mg QD for at least 12 weeks prior to the Screening Visit.

Table 1. High-Intensity vs. Moderate-Intensity Classifications

High-Intensity Dosage (QD)	Moderate-Intensity Dosage (QD)
Atorvastatin 40 mg, 80 mg	Atorvastatin 10 mg, 20 mg
Rosuvastatin 20 mg, 40 mg	Rosuvastatin 5 mg, 10 mg
	Simvastatin 20 mg, 40 mg

Approximately 104 subjects, including those with HeFH and ASCVD will be randomized into the study, with 52 (26 gemcabene 600 mg; 26 placebo) subjects on baseline high-intensity statins and 52 (26 gemcabene 600 mg; 26 placebo) subjects on baseline moderate-intensity statins. 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), a Screening Visit, a Treatment Period, and a Follow-up Visit.

A wash-out period will be required for eligible subjects taking any lipid-regulating therapies or supplements, with the exception of atorvastatin (10 mg, 20 mg, 40 mg or 80 mg QD), rosuvastatin (5 mg, 10 mg, 20 mg or 40 mg QD) or simvastatin (20 mg or 40 mg QD), 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 prior to the Screening Visit based on the duration of the wash-out period required. 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 or other lipid-regulating therapies such as bile acid sequestrants will require a 4-week wash-out period prior to the Screening Visit.

All eligible subjects will participate in the Screening Visit up to 14 days prior to Day 1. For eligible subjects taking the required stable statin therapy for ≥12 weeks and who do not require a wash-out period, the Screening Visit will be their first study visit.

The duration of the Treatment Period will be 12 weeks. Eligible subjects will be randomized via an interactive web/voice response system (IWRS/IVRS) on Day 1 in a 1:1 ratio to the following treatment groups: placebo or gemcabene 600 mg. Subjects will be stratified by statin intensity (as defined in Table 1) and Type 2 diabetes (yes or no). Subjects defined as diabetic will be those receiving concomitant anti-diabetic medication at screening. Randomization within a baseline statin intensity stratum will be capped at 52 subjects; once 52 subjects are randomized into a baseline statin intensity stratum, no further subjects in that statin intensity will be randomized (subjects in the other baseline statin intensity stratum will continue to be randomized until there are 52 randomized subjects in that stratum). By also stratifying on baseline diabetes

(yes, no), diabetic subjects will be evenly distributed across the treatment groups and statin-intensity subgroups. The first dose of study drug will be administered at the site on Day 1. On days with a scheduled office visit with blood sample collection, subjects will remain fasted (at least 10 hours) and should not take gemcabene until after the blood samples are collected. For days when the subject will self-dose, subjects will be instructed to take study drug at the same time in the morning with a full glass (8 ounces) of water either with or without food.

Post-randomization clinic visits will occur at Week 2, Week 4, Week 8 and Week 12. The Follow-up Visit will occur 4 weeks (±3 days) after the last dose of study drug.

3.2 Study Indication(s)

The indication for this study is for the treatment of hypercholesterolemia, including subjects, with or without Type 2 diabetes, with heterozygous familial hypercholesterolemia (HeFH) and subjects with atherosclerotic cardiovascular disease (ASCVD) not adequately controlled on stable statin therapy.

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 (neither pregnant or lactating) ≥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 throughout the duration of the study and for 8 days after the last dose of study drug.
3. Currently on a stable, low-fat, low-cholesterol diet in combination with allowed statin doses as described in Table 1, with or without ezetimibe 10 mg QD for at least 12 weeks prior to the Screening Visit;
4. Fasting LDL-C value ≥100 mg/dL (2.59 mmol/L) at the Screening Visit;
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;
7. Subjects with Type 2 diabetes who take anti-hyperglycemic agents 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:

1. Abnormal liver function test at the Pre-Screening Visit or the Screening Visit (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;
2. Moderate (Grade B) or severe (Grade C) chronic hepatic impairment according to the Child-Pugh classification;

3. 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;
4. Triglyceride value ≥500 mg/dL (5.65 mmol/L) at the Pre-Screening Visit or the Screening Visit;
5. Moderate to severe renal insufficiency defined as an estimated GFR <60 mL/min/1.73m^2 (calculated using The Chronic Kidney Disease Epidemiology Collaboration equation) at the Pre-Screening Visit or the Screening Visit;
6. Abnormal urinalysis (proteinuria greater than trace or any male or non-menstruating female with greater than trace hematuria), confirmed by reflexive urine protein:creatinine ratio testing;
7. 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;
8. Type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus (hemoglobin A1c [HbA1c]) value >8.5% based on results from the Pre-Screening Visit or the Screening Visit, or taking a thiazolidinedione (ie, pioglitazone or rosiglitazone);
9. New York Heart Association Class III or IV heart failure (see Appendix C);
10. 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. Subjects with adequately treated stable angina, per Investigator assessment, may be included;
11. Uncontrolled cardiac arrhythmia or prolonged QT on the Screening Visit or Day 1 prior to dosing ECG (QTcF >450 msec for men and >470 msec for women) or known family history of prolonged QT or unexplained sudden cardiac death;
12. Uncontrolled hypertension, defined as sitting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg, and confirmed by repeat measurement;
13. Currently receiving cancer treatments or, in the Investigator's opinion, at risk of relapse for recent cancer;
14. Inadequate wash-out of a PCSK9 inhibitor (8 weeks prior to the Screening Visit), a fibrate lipid-regulating agent (6 weeks prior to the Screening Visit), niacins (4 weeks prior to the Screening Visit), or other lipid-regulating therapies such as bile acid sequestrants (4 weeks prior to the Screening Visit);
15. Hypersensitivity to or a history of significant adverse reactions to any fibrate lipid-regulating agent;
16. Use of any excluded medications or supplements (e.g., potent cytochrome P450 [CYP] 3A4 inhibitors, see Appendix D);
17. History of drug or alcohol abuse within the past year or inability to comply with protocol requirements, including subject restrictions (see Section 5.6.3);

18. Previously treated with gemcabene (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
19. 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 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 prohibited 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 the regulatory authority.

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).

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 10% dropout rate in the study.

5 STUDY TREATMENTS

5.1 Treatment Groups

Subjects will be randomized on Day 1 in a 1:1 ratio to the following treatment groups: placebo or gemcabene 600 mg. Subjects are required to be on either a high-intensity statin therapy as defined in Table 2 (atorvastatin 40 mg or 80 mg QD; or rosuvastatin 20 mg or 40 mg QD) or a moderate-intensity statin therapy (atorvastatin 10 mg or 20 mg QD; rosuvastatin 5 mg or 10 mg QD; or simvastatin 20 or 40 mg QD) with or without ezetimibe 10 mg QD for at least 12 weeks prior to the Screening Visit. Subjects will be stratified by baseline statin intensity (high-intensity; moderate-intensity) and diabetes (yes or no).

Table 2. High-Intensity vs. Moderate-Intensity Classifications

High-Intensity Dosage (QD)	Moderate-Intensity Dosage (QD)
Atorvastatin 40 mg, 80 mg	Atorvastatin 10 mg, 20 mg
Rosuvastatin 20 mg, 40 mg	Rosuvastatin 5 mg, 10 mg
	Simvastatin 20 mg, 40 mg

5.2 Dose Rationale

Gemcabene was observed to be well tolerated at single doses up to 1500 mg and multiple doses up to 900 mg. This included 837 healthy subjects and subjects with varying underlying conditions who received multiple doses of up to 900 mg for up to 12 weeks. Adverse events were generally mild to moderate in intensity with no treatment-related SAEs reported.

Gemcabene dose response analysis on LDL-C in individual studies as well as across Phase 2 studies indicate gemcabene 600 mg is the optimal dose to move forward for testing in Phase 3. What is not known is the ability of gemcabene at its optimal dose (600 mg) to provide clinically and statistically meaningful LDL-C lowering in subjects not at goal (LDL-C ≥100 mg/dL) while receiving maximum statin therapy, including high-intensity statin and moderate-intensity statin therapy. Therefore, the current study will assess the effect of gemcabene 600 mg on LDL-C and other lipids and hsCRP in subjects whose LDL-C ≥ 100 mg while on stable statin therapy, of which 50% will be high-intensity and 50% will be moderate- intensity. Efficacy and safety data from this study will be used along with the integrated analysis work from previously completed studies to evaluate and confirm gemcabene 600 mg for use in Phase 3 studies.

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 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

At the initiation of the study, the Investigator will be instructed on the method for breaking the blind. Each clinical site will be supplied with an IWRS/IVRS unblinding code that will be allowed for emergency unblinding of an individual subject via the IWRS/IVRS. Blinding is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of subject safety. Unblinding at the clinical site for any other reason will be considered a protocol deviation. The Investigator should contact the Medical Monitor before breaking the blind. When the blind is broken, the reason must be fully documented. The Investigator and/or designee will be responsible for ensuring the IWRS/IVRS unblinding code is stored safely in a secure, readily accessible and known location, with access limited to those individuals authorized by the Investigator in case of an emergency.

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 (20 ±5°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 will be manufactured.

Study drug will be prepared as 7-day blister packages with each day's segment containing 3 tablets based on the treatment group:

- 600 mg: two 300 mg gemcabene tablets and 1 placebo tablet,
- Placebo: 3 placebo tablets.

5.5.3 Study Drug Preparation and Dispensing

Study drug will be administered at the site on Day 1 and on other clinic visit days. 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 but remembers within 6 hours, 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.

Plasma samples collected for potential pharmacokinetic analysis may be assayed to assess compliance.

5.5.6 Storage and Accountability

The study drug will be stored at room temperature (20 ±5°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, low-fat, low-cholesterol diet in combination with the allowed statins and doses as described in Table 1 for at least 12 weeks prior to the Screening Visit and through the duration of the study. Subjects may be on ezetemibe 10 mg QD, but are not required to be. Subjects with Type 2 diabetes who receive pharmacologic treatment must be on a stable regimen for 3 months prior to signing informed consent and not expected to change throughout the duration of study participation. 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 (4 weeks prior to the Screening Visit). Subjects are not permitted to use strong CYP3A4 inhibitors while on the study drug. See Appendix D for a specific 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 repeat blood testing.

Subjects are restricted from using alcohol within 48 hours prior to study visits.

Assessments that require a subject 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. 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. For days when the subject will self-dose, the subject will be instructed to take study drug at the same time in the morning with a full glass (8 ounces) of water either with or without food.

Subjects will be counseled on maintaining a low-fat, low-cholesterol diet (National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP-III] or equivalent) throughout the study.

5.6.4 Documentation of Prior and Concomitant Medication Use

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

The Investigator should record the use of all concomitant medications taken during the study, both prescribed and over the counter, in the 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.

6 STUDY PROCEDURES

A tabular listing of the Schedule of Procedures can be found in Appendix A. Assessments that require that a subject 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 ad lib.

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.

A wash-out period will be required for eligible subjects taking any lipid-regulating therapies or supplements, with the exception of atorvastatin (10 mg, 20 mg, 40 mg or 80 mg QD), rosuvastatin (5 mg, 10 mg, 20 mg or 40 mg QD), simvastatin (20 mg or 40 mg QD) 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 prior to the Screening Visit based on the duration of the wash-out period required. 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 or other lipid-regulating therapies such as bile acid sequestrants will require a 4-week wash-out period prior to the Screening Visit.

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 diabetes pharmacologic therapy for subjects with Type 2 diabetes;
- Perform full physical examination;
- Record vital signs, height, weight and calculate BMI;
- Collect urine sample for urinalysis;
- 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 LDL-C (LDL-C ultracentrifugation in subjects with TG $\geq$ 400 mg/dL) and TG;
- Initiate wash-out;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent); and

- Assess adverse events (SAEs that occur prior to the first dose of study drug [Day 1] should be reported as an update to medical history as well as be reported on the appropriate adverse event eCRF) and concomitant medications.

6.3 Screening Visit (up to Day -14)

All eligible subjects will participate in the Screening Visit up to 14 days prior to Day 1. Subjects must fast (at least 10 hours) prior to this visit.

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.

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.

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

- Obtain informed consent;
- Confirm eligibility based on inclusion/exclusion criteria;
- Obtain medical/surgical history and demographics;
- If applicable, document diagnosis of HeFH as:
  - Clinical diagnosis; per Simon Broome criteria for definite FH or the WHO/Dutch Lipid Network criteria with a score >8 points or;
  - Genotyping;
- If applicable, document diagnosis of ASCVD for those subjects with:
  - A history of myocardial infarction, prior coronary angiography showing ≥ 75% stenosis of at least one epicardial coronary vessel, or prior coronary revascularization procedures (either percutaneous coronary intervention or coronary artery bypass graph);
- Obtain concomitant medications; including all anti-hyperglycemic agents 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 for urinalysis including urine protein:creatinine ratio and albumin:creatinine ratio;
- 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 (including LDL-C ultracentrifugation, for subjects with TGs ≥ 400 mg/dL);
- Perform 12-lead ECG;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent); and
- Assess adverse events (SAEs that occur prior to the first dose of study drug [Day 1] should be reported as an update to medical history as well as be reported on the appropriate adverse event eCRF) and concomitant medications.

6.4 Treatment Period (Visit T1 through Visit T5)

Subjects must fast (at least 10 hours) prior to each visit.

6.4.1 Visit T1 (Day 1)

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

- Perform symptom-directed physical examination;
- Determine if there have been any changes in the subject's health affecting eligibility;
- Record vital signs and weight;
- Collect urine sample for urinalysis including urine protein:creatinine ratio, albumin:creatinine ratio and neutrophil gelatinase-associated lipocalin (NGAL);
- 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 (including LDL-C ultracentrifugation, for subjects with TGs ≥ 400 mg/dL) and apolipoproteins;
  - Fasting insulin and FPG;
  - CI [redacted]
  - hsCRP, serum amyloid A (SAA), adiponectin, and fibrinogen; and
  - Reserve samples;
- Perform 12-lead ECG;
- Randomize subjects via IVRS/IWRS;
- Dispense study drug and instructions;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent);
- Assess adverse events and update concomitant medications; and
- Administer study drug (study drug will be administered at the site on 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
  - Reserve samples;
- Perform 12-lead ECG;
- Assess and document study drug compliance;
- Dispense study drug and instructions;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent);
- Assess adverse events and update concomitant medications; and
- Administer study drug (subjects will self-dose).

6.4.3 Visit T3 (Week 4)

The following procedures will be performed at Visit T3 (Week 4; Day 29 ±3 days):

- Perform symptom-directed physical examination;
- Record vital signs and weight;
- Collect urine sample for urinalysis including urine protein:creatinine ratio, albumin:creatinine ratio and NGAL;
- 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 ultracentrafugation (in subjects with TG ≥ 400 mg/dL) and apolipoproteins; and
  - Reserve samples;
- Perform 12-lead ECG;
- Assess and document study drug compliance;
- Dispense study drug and instructions;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent);
- Assess adverse events and update concomitant medications; and

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

6.4.4 Visit T4 (Week 8)

The following procedures will be performed at Visit T4 (Week 8; Day 57 ±3 days):

- Perform symptom-directed physical examination;
- Record vital signs and weight;
- Collect urine sample for urinalysis;
- 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 ultracentrifugation (in subjects with TG ≥ 400 mg/dL) and apolipoproteins;
  - Reserve samples;
- Perform 12-lead ECG;
- Assess and document study drug compliance;
- Dispense study drug and instructions;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent);
- 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; Day 85 [can be performed up to 3 days prior to Day 85, but not after Day 85]):

- Perform full physical examination;
- Record vital signs and weight;
- Collect urine sample for urinalysis including urine protein:creatinine ratio, albumin:creatinine ratio and NGAL;
- 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/Day 85 will also be followed-up 2 weeks (±3 days) after the last dose of study drug in addition to the Week 4 (±3 days) Follow-up Visit), coagulation, and hematology;
  - Fasting lipid panel, LDL-C ultracentrifugation (in subjects with TGs ≥ 400 mg/dL) and apolipoproteins;
  - Fasting insulin and FPG

- [redacted]
- HbA1c;
- hsCRP, SAA, adiponectin and fibrinogen; and
- Reserve samples;

- Perform 12-lead ECG;
- Assess and document study drug compliance;
- Assess adverse events and update concomitant medications; and
- Administer study drug (subjects will self-dose).

6.5 Follow-up Visit (Day 113)

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 (Day 113 ±3 days):

- Perform symptom-directed physical examination (only for subjects who had an abnormal result at Week 12/Day 85 [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 12/Day 85 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event);
- Obtain blood sample for safety chemistry panel, coagulation, and hematology (only for subjects who had an abnormal result at Week 12/Day 85 [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

Subjects must fast (at least 10 hours) prior to this visit.

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;
- Collect urine sample for urinalysis including urine protein:creatinine ratio, albumin:creatinine ratio and NGAL;
- 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, LDL-C ultracentrifugation (in subjects with TG ≥ 400 mg/dL) and apolipoproteins;
  - Fasting insulin and FPG
  - CI [redacted]
  - HbA1c;
  - hsCRP, SAA, adiponectin and fibrinogen; and
  - Reserve samples;
- Perform 12-lead ECG;
- Assess and document study drug compliance; 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 LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), TG, HDL-C, and VLDL-C at baseline, Week 2, Week 4, Week 8, and Week 12;
- Fasting ApoB, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, ApoE and Lp(a) at baseline, Week 4, Week 8 and Week 12;
- hsCRP, SAA, adiponectin and fibrinogen at baseline and Week 12;
- Framingham Risk Score and NCEP ATP-III Risk at baseline and Week 12;
- CI

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 (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 (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 (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 (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 (Day 1) should be reported in the medical history. Any SAEs occurring prior to the first dose of study drug (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 (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 (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 EDC 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 >0.3 mg/dL (27 μmol/L) from baseline or a GFR decrease of >15 mL/min from baseline is observed, a repeat chemistry 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 values at the time of assessment but may require additional or closer/follow-up monitoring of renal studies.

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.

8.2 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 insubject hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

- NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the 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 patient 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 patient 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 patient 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 PI within 24 hours of awareness on the Exposure In Utero form.

A patient 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 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 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 ad lib.

Central laboratory results will be provided to the sites, with the exception of the post-randomization lipid values. 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.

At the Pre-Screening Visit, if applicable, fasting LDL-C and TG will be measured. A full fasting lipid panel will be assessed at all other study visits, excluding the Follow-up Visit. Fasting apolipoproteins will be assessed at Day 1, Week 4, Week 8, Week 12, and the ET Visit, if applicable. In addition to these lipid parameters, CI [redacted] hsCRP, SAA, adiponectin, FPG, fasting insulin, and fibrinogen will also be measured at Day 1, Week 12, and the ET Visit, if applicable.

A urine sample for urinalysis will be collected at the Pre-Screening Visit, if applicable, the Screening Visit, Day 1, Week 4, Week 8, 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. A urine microscopic examination will be performed when the dipstick result is abnormal (positive for blood, leukocyte esterase, or nitrites). Urine protein:creatinine ratio and albumin:creatinine ratio will be performed at the Screening Visit, Day 1, Week 4, 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 Day 1, Week 4, 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.

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, Day 1, Week 2, Week 4, and Week 8.

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.

HbA1c will be measured 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.

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 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 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, Day 1, Week 2, Week 4, Week 8, 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), Day 1, Week 2, Week 4, Week 8, 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 Screening Visit.

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 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

Reserve samples will be collected for the optional assay of exploratory biomarkers or pharmacokinetic assessments. Reserve 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, repeat lipid testing, and/or repeat or additional clinical laboratory and urine testing in the event of a safety issue. The reserve samples collected on Visits 3 and 5 may be used for assay of plasma drug concentrations (PK Analysis). The PK concentration values be used to confirm subject compliance, summarize of observed plasma concentrations, or a model based population pharmacokinetic analysis.

9 STATISTICS

9.1 Sample Size

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C, with the primary focus on the overall set of randomized subjects. The efficacy within each baseline statin intensity (high-intensity; moderate-intensity) stratum is also of interest for this study; thus, the study is powered for the analyses within each baseline statin intensity stratum. A sample size of 26 randomized subjects in the gemcabene 600 mg group and 26 randomized subjects in the placebo group within each baseline statin intensity stratum is expected to provide 80% power to detect a difference of 17% in the percent change from baseline to Week 12 in LDL-C between the gemcabene treatment group and the placebo group within each baseline statin intensity stratum. This calculation is based on a 2-sided t-test at the 5% level of significance ($\alpha = 0.05$), a common standard deviation of 20, and a drop-out rate of 10%. The sample size of 26 randomized subjects in each baseline statin intensity stratum in the gemcabene 600 mg group gives a total of 52 randomized subjects in the gemcabene 600 mg group. Twenty-six randomized subjects in each baseline statin intensity stratum in the placebo group gives a total of 52 randomized subjects in the placebo group. Thus, the total study sample size is 104 randomized subjects.

There are no planned interim analyses in the study.

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. 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 treatment unblinding at the end of the study.

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 the 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 LDL-C from baseline to Week 12. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA) with percent change from baseline to Week 12 in LDL-C as the dependent variable; treatment, baseline statin intensity (high-intensity; moderate-intensity), and baseline diabetes (yes or no) as factors; and baseline fasting LDL-C as a covariate. Baseline will be defined as the average of the LDL-C values at Screening/Visit S1 and pre-dose Day 1/Visit T1. The ANCOVA will be performed using the FAS, with subjects included in their randomized treatment group regardless of the treatment they actually received. Missing values for Week 12 will be imputed using last observation carried forward (LOCF); only post-baseline values will be used for the imputation. The least-squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI), and associated p-value. A 2-sided test with a significance level of 0.05 will be used for the comparison of gemcabene 600 mg 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 and exploratory efficacy analyses

Secondary efficacy endpoints include:

- Percent change from baseline to Week 12 in LDL-C for each statin intensity stratum (high-intensity; moderate-intensity);
- Change from baseline to Week 2, Week 4, Week 8, and Week 12 in LDL-C;
- Change and percent change from baseline to the average of Week 8 and Week 12 measurements in LDL-C;
- Change and percent change from baseline to Week 12 in LDL-C in subjects on and not on ezetimibe;
- Change and percent change from baseline to Week 2, Week 4, Week 8, and Week 12 in non-HDL-C, TC, TG, HDL-C and VLDL-C;
- Percent of subjects achieving LDL-C reduction of ≥ 10%, ≥ 15%, and 20% at Week 4, Week 8, and Week 12;
- Percent of subjects achieving an LDL-C value < 100 mg/dL (2.59 mmol/L) at Week 4, Week 8, and Week 12;
- Change and percent change from baseline to Week 4, Week 8 and Week 12 in Apo B, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, ApoE and Lp(a);
- Change and percent change from baseline to Week 4, Week 8 and Week 12 in hsCRP, SAA, adiponectin, and fibrinogen;
- Change from baseline to Week 12 in Framingham Risk score; and

- Change from baseline to Week 12 in NCEP ATP-III Risk.

The exploratory efficacy endpoints include:

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

Analysis of secondary and exploratory endpoints will not be adjusted for multiplicity. Each of the secondary and exploratory endpoints will be compared to a significance level of 0.05. Given the large number of endpoints, p-values for the secondary and exploratory endpoints will be considered descriptive.

For continuous secondary and exploratory efficacy endpoints related to change/percent change in basic fasting lipids, lipoproteins, hsCRP, SAA, fibrinogen, adiponectin, FPG, fasting insulin and CI [redacted] the same ANCOVA for the primary efficacy endpoint will be used, with the respective baseline included as the covariate. Note that for secondary endpoints such as change from baseline in LDL-C within the moderate-intensity stratum, the ANCOVA model will not include a term for baseline statin intensity stratum. Baseline for TC, non-HDL-C, HDL-C and VLDL-C are defined similarly to baseline for LDL-C. Baseline for fasting lipoproteins, hsCRP, SAA, fibrinogen, adiponectin, FPG, fasting insulin and serum CI [redacted] are defined as the value from pre-dose Day 1/Visit T1. Baseline for HbA1c is the value from the first visit (Pre-Screening or Screening Visit).

Each ANCOVA will be performed using the FAS (or the specific subgroup within the FAS that is indicated in the specific endpoint [e.g. subgroup of baseline high-intensity statin subjects]), with subjects included in their randomized treatment group regardless of the treatment they actually received. Missing values for post-randomization time points will be imputed using LOCF; only post-baseline values will be used for the imputation. The output from each ANCOVA will include the LSM and SE for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value. 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 LDL-C reduction of $\geq$ 10%, $\geq$ 15% and $\geq$ 20% at Week 4, Week 8, and Week 12 will each be analyzed using a logistic regression with treatment, baseline statin intensity (high-intensity; moderate-intensity), baseline diabetes (Y/N) and baseline LDL-C value as independent factors. For each analysis, the percent of subjects in each treatment group meeting the criteria, the odds ratios with 95% CI, and p-value will be provided. The percent of subjects achieving a LDL-C value <100 mg/dL (2.59 mmol/L) at Week 4, Week 8, and Week 12 will be analyzed in the same manner, with similar output provided for each endpoint. For all of these endpoints, the FAS will be used, with subjects included in their randomized treatment group regardless of the treatment they actually received.

Framingham Risk scores and estimated 10-year risk will be summarized at baseline and Week 12. Additionally, the change from baseline to Week 12 in Framingham Risk scores and estimated 10-year risk will be summarized. The number and percent of subjects in each NCEP ATP-III Risk category will be summarized at baseline and Week 12. Also, a shift table of NCEP ATP-III Risk categories from baseline and Week 12 will be provided. The FAS, with subjects included in their randomized treatment group regardless of the treatment they actually received, will be used for all of these summarizations. Finally, CI [redacted]

Confirmatory analysis of the secondary and exploratory endpoints will be performed using the PPS.

9.3.2 Analysis of Safety

No statistical analysis of safety data will be performed in this study. Safety will be assessed using the SAS with subjects included in the treatment group they actually received, regardless of their randomized treatment. The assessment of safety will include adverse events, clinical laboratory assessments, ECGs, physical examinations, and vital signs. Observed case data will be used.

Adverse events (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. Change from baseline to each time point, if appropriate, will also be summarized by treatment group. Baseline for safety laboratory data will be defined as the last pre-dose measurement (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 measurement (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 MedDRA for medical history and adverse events, and
- World Health Organization 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 Subject Card

On enrollment in the study, the subject will receive a subject card to be carried at all times. The subject card will state that the subject is participating in a clinical research study, type of treatment, number of treatment packs received, and contact details in case of an SAE.

11.5 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.

11.6 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.

11.7 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.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. 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.

11.9 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.

11.10 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.

11.11 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.

11.12 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.

11.13 Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of 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, 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, Michigan 48152
Telephone: +1-248-681-9815
Facsimile: +1-734-864-5765

12.2.2 Contract Research Organization

PI

12.2.3 Biological Specimens

PI

13 REFERENCES

1. Pedersen TR, Kjekshus J, Berg K, et al.; Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. Atheroscler Suppl. 2004 Oct;5(3):81-7.
2. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995 Nov 16;333(20):1301-7.
3. Sacks FM, Pfeffer MA, Moye LA, et al.; Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med. 1996 Oct 3;335(14):1001-9.
4. Stone NJ, Robinson JG, Lichtenstein AH, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45.
5. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA. 2003 Apr 2;289(13):1681-90.

APPENDIX A: SCHEDULE OF PROCEDURES

	Pre-Screening[a]	Screening[b]	Treatment Period[c]					Follow-up[d]	ET
		up to Day -14	Day 1[e]	Week 2 (Day 15± 3 days)	Week 4 (Day 29± 3 days)	Week 8 (Day 57± 3 days)	Week 12 (Day 85, or up to 3 days earlier)	Day 113 ± 3 days	
		Visit S1	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5		
Informed consent	X	X[f]							
Inclusion/exclusion criteria	X	X							
Medical/surgical history and demographics	X	X[f]							
Full physical examination[g]	X	X[f]					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
Body Mass Index (BMI)	X	X							
Urinalysis[l]	X	X	X		X	X	X	X[i]	X
Serum/urine pregnancy test[m]	X	X	X	X	X	X	X		X
Safety chemistry panel, coagulation, and hematology[n]	X	X	X	X	X	X	X	X[i]	X
TSH, HbA1c, and serology[o]	X	X[f]					X		X
Fasting lipid panel[p]; LDL-C ultracentrifugation when necessary	X[q]	X	X	X	X	X	X		X
Fasting apolipoproteins[r]			X		X	X	X		X
[redacted]			X				X		X
hsCRP, SAA,fibrinogen, and adiponectin			X				X		X
Fasting plasma glucose, insulin			X				X		X
Randomization			X						
Study drug administration[s]			X	X	X	X	X		
Dispense study drug and instructions			X	X	X	X			
Compliance check				X	X	X	X		X
Dietary instructions[t]	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

Concomitant medications	X	X[f]	X	X	X	X	X	X	X
Reserve samples			X	X	X	X	X		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 or other lipid-regulating therapies such as bile acid sequestrants 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 14 days prior to Day 1. For subjects taking the required stable statin therapy for >4 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 Day 1 through Week 8. Week 12 assessments can be performed up to 3 days prior to Week 12, but not after Week 12.
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 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. A urine microscopic examination will be performed when the dipstick result is abnormal (positive for blood, leukocyte esterase, or nitrites). Urine protein:creatinine ratio (albumin:creatinine) will be performed at the Screening Visit, Day 1, Week 4, 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 Day 1, Week 4, 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.
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, Day 1, Week 2, Week 4, and Week 8.
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 Week 4 (±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. Only HbA1c will be measured at Week 12, and the ET Visit, if applicable.
p. Includes LDL-C, non-HDL-C, TC, TG, HDL-C, and VLDL-C. 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.
q. Includes LDL-C and 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.
r. Includes ApoB, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, ApoE, and Lp(a). Fasting will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Subjects will be permitted to have water.
s. Study drug will be administered at the site on Day 1. Subjects will self-dose at all other times during the Treatment Period.
t. Subjects will be counseled on a low-fat, low-cholesterol diet (NCEP ATP-III guidelines or equivalent).
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 (Day 1) should be reported as an update to medical history as well as be reported on the appropriate adverse event eCRF.

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; CI [redacted] CI 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 Parameter

Glycosylated hemoglobin (HbA1c)
Fasting plasma glucose
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 (and albumin:creatinine ratio) will be performed at the Screening Visit, Day 1, Week 4, 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.
3. Urinary NGAL will be measured at Day 1, Week 4, 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.

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:

Apolipoprotein (Apo) A-I	ApoA-II
ApoB	ApoA-V
ApoC-III	ApoE
ApoC-II	Lipoprotein (a)
High-density lipoprotein cholesterol	Low-density lipoprotein cholesterol
Non-high-density lipoprotein cholesterol	Very low-density lipoprotein cholesterol
Triglycerides	Total cholesterol
High-sensitivity C-reactive protein	Serum amyloid A
CCI	Fibrinogen
Adiponectin	

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: CYTOCHROME P450 3A4 INHIBITORS: 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.