Title: A Phase 2 Open-Label, Dose-Finding Study to Assess the Efficacy, Safety, and Tolerability of Gemcabene in Patients with Homozygous Familial Hypercholesterolemia on Stable, Lipid-Lowering Therapy (COBALT-1)

NCT ID: NCT02722408

Approval Date: 19-Feb-2016

16. APPENDICES

APPENDIX 16.1: STUDY INFORMATION

APPENDIX 16.1.1: PROTOCOL AND PROTOCOL AMENDMENTS

CLINICAL STUDY PROTOCOL

A Phase 2 Open-Label, Dose-Finding Study to Assess the Efficacy, Safety, and Tolerability of Gemcabene in Patients with Homozygous Familial Hypercholesterolemia on Stable, Lipid-Lowering Therapy (COBALT-1)

Investigational Product: Gemcabene calcium tablets (gemcabene)
Protocol Number: GEM-201

Sponsor:
Gemphire Therapeutics Inc.
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Version Number: 1.0
Date: 19 February 2016

SIGNATURE PAGE

STUDY TITLE: A Phase 2 Open-Label, Dose-Finding Study to Assess the Efficacy, Safety, and Tolerability of Gemcabene in Patients with Homozygous Familial Hypercholesterolemia on Stable, Lipid-Lowering Therapy (COBALT-1)

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

Signature	Date
PI	19 FEB 2016
Gemphire Therapeutics Inc.	
PI	19FEB 2016
PI	19Feb2016

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 patients.

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

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 2 Open-Label, Dose-Finding Study to Assess the Efficacy, Safety, and Tolerability of Gemcabene in Patients with Homozygous Familial Hypercholesterolemia on Stable, Lipid-Lowering Therapy (COBALT-1)

PROTOCOL NUMBER: GEM-201

INVESTIGATIONAL PRODUCT: Gemcabene calcium tablets (gemcabene)

PHASE: 2

INDICATION(S): For the treatment of hypercholesterolemia, specifically patients with homozygous familial hypercholesterolemia (HoFH)

OBJECTIVES:

The primary objective of this study is to evaluate the efficacy, safety, and tolerability of multiple doses of gemcabene in patients with HoFH on stable, lipid-lowering therapy.

The secondary objectives of this study are the following:

- To confirm the appropriate dose for use in Phase 3 registration studies as assessed by efficacy, pharmacokinetic (PK), and safety data (an effective dose is defined as a dose that achieves ≥15% mean reduction in low-density lipoprotein cholesterol [LDL-C] after 4 weeks of treatment);
- To further evaluate the efficacy of gemcabene in patients with HoFH following 4 weeks of dosing with gemcabene 300 mg once daily (QD), 4 weeks of dosing with gemcabene 600 mg QD, and 4 weeks of dosing with gemcabene 900 mg QD, as assessed by measurements of lipid and apolipoprotein parameters, high-sensitivity C-reactive protein (hsCRP), and fibrinogen; and
- To evaluate trough plasma concentrations of gemcabene at doses 300 mg, 600 mg, and 900 mg.

CI [redacted]

POPULATION:

The population for this study is male and female patients, ≥17 years of age, diagnosed with HoFH by genetic confirmation or a clinical diagnosis based on either (1) a history of an untreated LDL-C concentration >500 mg/dL (12.92 mmol/L) together with either appearance of xanthoma before 10 years of age, or evidence of heterozygous familial hypercholesterolemia in both parents or, if history is unavailable, (2) LDL-C >300 mg/dL (7.76 mmol/L) on maximally tolerated lipid-lowering drug therapy. Patients must have a fasting LDL-C value >130 mg/dL (3.36 mmol/L) and a triglyceride (TG) value ≤400 mg/dL (4.52 mmol/L) at the Screening Visit while on a stable, low-fat, low-cholesterol diet in combination with a pre-existing,

regulatory-approved, not excluded lipid-lowering therapy (i.e., statins, monoclonal antibodies to PCSK9, cholesterol-absorption inhibitors, bile acid sequestrants, or nicotinic acid, or any combination thereof).

STUDY DESIGN AND DURATION:

This is a Phase 2, open-label, dose-finding, 3-period, 3-treatment study using successively escalating doses of 300 mg, 600 mg, and 900 mg gemcabene in patients with HoFH. All patients will be on each of the successive doses for 4 weeks at a time. Patients will remain on their current stable, lipid-lowering therapy throughout the study. Patients will not be allowed in the study if they are undergoing apheresis or taking mipomersen or lomitapide.

Efficacy, PK, and safety data from this study will be used along with previously completed studies and a planned randomized, placebo-controlled study in patients with hypercholesterolemia (GEM-301) to confirm the appropriate dose of gemcabene for use in Phase 3 studies. An effective dose is defined as a dose that achieves ≥15% mean reduction in LDL-C after 4 weeks of treatment with the study totaling 12 weeks of treatment.

Approximately 8 patients will be enrolled into the study. Total study duration will be up to 18 weeks and will consist of a Screening Visit, a Treatment Period, and a Follow-up Visit.

The Screening Visit will occur up to 14 days prior to Day 1. Patients will sign the informed consent form prior to any study procedures being performed. Patients must meet all of the inclusion and none of the exclusion criteria to be eligible for study participation.

The Treatment Period is a sequential design whereby each patient will receive gemcabene 300 mg QD for 4 weeks. The same patients will then receive a 600 mg dose QD for 4 weeks and finally 900 mg dose QD for 4 weeks. There will be no interruptions in gemcabene dosing when changing from the 300 mg to the 600 mg dose or when changing from the 600 mg to the 900 mg dose unless there are clinically significant safety issues resulting in the temporary or permanent discontinuation of study drug. The first 300 mg dose of study drug will be administered at the site on Day 1. For days when patients will self-dose, they will be instructed to take study drug at the same time each morning on an empty stomach 30 to 60 minutes prior to breakfast. For patients also taking bile acid sequestrants, study drug should be taken at least 2 hours before administration of bile acid sequestrants. Assessments will be performed after the patient has been on the study drug for 2 weeks for each dosing level and on the last day of each dose.

For each escalated dose, percent change from baseline in LDL-C will be calculated using the baseline LDL-C value and the final LDL-C value measured for each dose. Baseline will be defined as the average of the Screening Visit occurring up to 14 days prior to Day 1 and Day 1 (pre-dose) measurements.

Pharmacokinetic samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose) and 0.5, 1, 2, 3, 5, and 12 hours post-dose on Day 28, Day 56, and Day 84 in collection tubes containing dipotassium ethylenediaminetetraacetic acid as the anticoagulant; for determination of gemcabene repeat-dose PK parameters, steady state is assumed following QD administration for 28 days and therefore, plasma gemcabene concentrations at 24 hours post-dose are considered to be equal to pre-dose concentrations. For all other study visits where routine plasma drug monitoring will be performed (Day 1, Day 14, Day 42, Day 70, and the Early Termination Visit,

if applicable), samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose if a previous day's dose occurred).

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 packaged in high-density polyethylene bottles with child-resistant closures. Patients will take the following for each of the 3 dose levels:

- 300 mg: one 300 mg tablet orally QD,
- 600 mg: two 300 mg tablets orally QD, and
- 900 mg: three 300 mg tablets orally QD.

Patients will be instructed to take study drug at the same time in the morning on an empty stomach 30 to 60 minutes prior to breakfast. For patients also taking bile acid sequestrants, study drug should be taken at least 2 hours before administration of bile acid sequestrants.

EFFICACY VARIABLES:

The primary efficacy analysis is the percent change in LDL-C from baseline to Day 28, Day 56, and Day 84.

The secondary efficacy analyses are the following:

- The change in LDL-C from baseline to Day 28, Day 56, and Day 84;
- The change and percent change in lipid parameters (non-high-density lipoprotein cholesterol [non-HDL-C], total cholesterol [TC], TG, high-density lipoprotein cholesterol [HDL-C], and very low-density lipoprotein cholesterol [VLDL-C]) from baseline to Day 28, Day 56, and Day 84;
- The change and percent change in lipid parameters (non-HDL-C, TC, TG, HDL-C, and VLDL-C) from baseline to Day 28, Day 56, and Day 84 according to the receptor mutation status;
- The number (%) of patients achieving LDL-C reduction of ≥15%, ≥20%, ≥25%, and ≥30% at Day 28, Day 56, and Day 84;
- The number (%) of patients achieving an LDL-C value <100 mg/dL (2.59 mmol/L) at Day 28, Day 56, and Day 84, and at any time during the study;
- The change and percent change in apolipoprotein (Apo) B, ApoA-I, ApoA-II, ApoC-II, ApoC-III, ApoE, and lipoprotein(a) from baseline to Day 28, Day 56, and Day 84;
- The change and percent change in hsCRP from baseline to Day 28, Day 56, and Day 84; and
- The change and percent change in fibrinogen from baseline to Day 28, Day 56, and Day 84.

CI [redacted]

PHARMACOKINETIC VARIABLES:

The following PK parameters will be calculated, as appropriate, from the individual plasma concentrations of gemcabene on Day 28, Day 56, and Day 84:

- C_{max}: maximum plasma concentration,
- t_{max} (h): time to maximum plasma concentration,
- AUC_{0-t} (ng·h/mL): area under the concentration-time curve to the last quantifiable time, and
- AUC_{0-24} (ng·h/mL): area under the concentration-time curve to the 24-hour time point.

SAFETY VARIABLES:

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, urinalysis sediments, pH, electrolytes), and skeletal muscle (i.e., creatine kinase) toxicities; 12-lead electrocardiograms (ECGs); physical examinations; and vital signs.

STATISTICAL ANALYSES:

Given the proposed crossover design of this study, a within-patient analysis can be performed for the comparison of dose groups. For continuous variables, the dose groups will be compared on their change and percent reduction from baseline (using their pre-treatment baseline value). A longitudinal analysis will be performed with a mixed-effects model repeated measures analysis including percent change in LDL-C as the dependent variable, visit as a fixed effect and patient as a random effect. The additional drug benefit with increasing dose will be estimated from the mixed-effects model. Least-squares mean differences and corresponding 95% confidence intervals, separately for each of the 3 paired comparisons (300 versus 600 mg, 300 versus 900 mg, and 600 versus 900 mg) will be provided. In addition, a scatterplot with regression curve fit of the percent reduction from baseline versus dose will be performed. For binary variables such as the percentage of patients, descriptive statistics will be calculated for each dose group.

The PK parameters will be calculated, as appropriate, from the individual plasma concentrations of gemcabene using a non-compartmental approach. Pharmacokinetic variables will be computed using WinNonlin Professional® or other appropriate software.

Safety will be assessed using the population of all patients who receive any amount of study drug. The assessment of safety will include adverse events, clinical laboratory assessments, ECGs, physical examinations, and vital signs. The safety analysis will be based primarily on the frequency of new or worsening adverse events, laboratory abnormalities, and serious adverse events. Other safety data will be summarized as appropriate.

Safety laboratory data will be summarized at baseline, Day 28, Day 56, and Day 84, and change from baseline to Day 28, Day 56, and Day 84. Frequency counts of new or worsening abnormalities will also be provided.

SAMPLE SIZE DETERMINATION:

The primary goal of the study is to assess the mean percent change in LDL-C from baseline over 12 weeks of treatment from the 3 dose levels. Dosing 8 patients per group will yield reasonable precision in estimation in mean change from baseline in LDL-C.

SITES: Approximately 9 sites worldwide, including the United States, Canada, and Israel.

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ALT	Alanine aminotransferase
Apo	Apolipoprotein
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the concentration-time curve to the 24-hour time point
AUC_{0-t}	Area under the concentration-time curve to the last quantifiable time
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CK	Creatine kinase
C_{max}	Maximum plasma concentration
CRA	Clinical research associate
CRP	C-reactive protein
CTA	Clinical trial authorisation
CYP	Cytochrome P450
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ET	Early Termination
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
HIV	Human immunodeficiency virus
HoFH	Homozygous familial hypercholesterolemia
hsCRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Affairs

Abbreviation	Definition
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	Pharmacokinetic
QD	Once daily
SAE	Serious adverse event
SOP	Standard Operating Procedure
TC	Total cholesterol
TG	Triglyceride
t_{max}	Time to maximum plasma concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein
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 (VLDL). Based on prior clinical studies, the combined effects for these mechanisms has been observed to result in a reduction of plasma VLDL cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), TGs, as well as an elevation in high-density lipoprotein cholesterol (HDL-C). Gemcabene has also been shown to markedly lower C-reactive protein (CRP).

Gemphire Therapeutics Inc. (Gemphire) is developing gemcabene as an adjunct to diet and statin therapy for the treatment of patients with dyslipidemia, including patients with Homozygous Familial Hypercholesterolemia (HoFH).

1.2 Rationale

Homozygous familial hypercholesterolemia is a rare, genetic disease that typically results when an individual inherits a substantial defect in clearance of low-density lipoprotein (LDL) particles, resulting in high and dangerous levels of LDL-C from birth. In patients with HoFH, LDL-C usually exceeds 500 mg/dL (12.92 mmol/L) prior to treatment, and the clinical outlook for untreated HoFH patients is bleak, with a life expectancy of not much more than 30 years.[1] Current treatment generally includes a combination of dietary intervention, lipid-regulating medications, and plasmapheresis or LDL-apheresis. However, even when combinations of therapies are utilized, the vast majority of patients still do not reach LDL-C levels considered optimal or consistent with halting the progression of coronary heart disease.

When administered in LDL receptor-deficient mice, a model of HoFH, gemcabene significantly reduced LDL-C both alone and in combination with atorvastatin.[2] Study results further suggest that the mechanism(s) for modulating plasma cholesterol by gemcabene may be independent of hepatic LDL receptors.

Three Phase 2 clinical studies in over 500 patients have been conducted with gemcabene to evaluate changes in lipid parameters in patients with hypercholesterolemia or dyslipidemia. Overall, these studies demonstrated that gemcabene doses of 300 mg to 900 mg significantly lowered LDL-C by approximately 20% to 30% when administered as monotherapy and when used as an adjunctive treatment in patients with uncontrolled hypercholesterolemia despite stable statin therapy. Across several studies, reduction in LDL-C has been accompanied by a reduction in apolipoprotein (Apo) B and CRP/high-sensitivity CRP (hsCRP), which are known to contribute to cardiovascular disease. These studies also demonstrated that gemcabene doses of 150 mg were less effective at lowering LDL-C. The current study seeks to demonstrate the effects of treatment with gemcabene on LDL-C and other lipid parameters in patients with HoFH.

1.3 Risk/Benefit

Depending on residual LDL receptor activity, patients often demonstrate a significantly limited response to otherwise highly efficacious statin therapy. Medications that have been approved specifically for the treatment of HoFH include lomitapide and mipomersen. Unfortunately, clinical

application of these therapies is limited, as both treatments carry a product label BOX WARNING for hepatotoxicity. In addition, patients are often unable to tolerate other side effects of these medications, including injection site reactions and flu-like symptoms associated with mipomersen and gastrointestinal discomfort associated with lomitapide.

Whereas compounds such as mipomersen and lomitapide act late in the process of VLDL assembly, gemcabene reduces the synthesis of lipids required for lipoprotein assembly earlier in the process.[3] This allows the precursors of cholesterol and fatty acid synthesis to be utilized in other metabolic processes without causing subsequent accumulation of intracellular TGs or hepatic fat leading to hepatic steatosis.

The recently Food and Drug Administration (FDA)-approved proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, Repatha™, has demonstrated substantial LDL-C-lowering ability, but because the mechanism of action is dependent upon the presence of LDL-C receptors with some residual function, the LDL-C-lowering effect is typically reduced in patients with HoFH compared to that seen in other populations.[4,5]

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

The clinical program conducted to date has demonstrated that gemcabene is well tolerated. A total of 895 healthy adult subjects and patients 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 once daily (QD). This includes 837 subjects who received multiple doses of up to 900 mg daily for up to 12 weeks. Safety of these subjects was evaluated by regular 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 significant drug-drug interactions have been observed with simvastatin (80 mg), atorvastatin (80 mg), or digoxin (0.25 mg). No clinically relevant effect on QTc interval 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 patients reported a treatment-emergent serious adverse event (SAE) across all previous studies. None of these SAEs were considered treatment-related. There were no deaths.

Small mean increases in serum creatinine and blood urea nitrogen (BUN) have been observed in some studies. These changes appeared within the first 2 to 4 weeks and did not appear to increase further over time. An iohexol clearance study showed that glomerular filtration rate (GFR) slightly decreased and was associated with a slight increase in serum creatinine. There was no indication of proteinuria or hematuria identified in any subject. There were no significant changes observed in urine protein, suggesting 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.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy, safety, and tolerability of multiple doses of gemcabene in patients with HoFH on stable, lipid-lowering therapy.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To confirm the appropriate dose for use in Phase 3 registration studies as assessed by efficacy, PK, and safety data (an effective dose is defined as a dose that achieves ≥15% mean reduction in LDL-C after 4 weeks of treatment);
- To further evaluate the efficacy of gemcabene in patients with HoFH following 4 weeks of dosing with gemcabene 300 mg QD, 4 weeks of dosing with gemcabene 600 mg QD, and 4 weeks of dosing with gemcabene 900 mg QD, as assessed by measurements of lipid and apolipoprotein parameters, hsCRP, and fibrinogen; and
- To evaluate trough plasma concentrations of gemcabene at doses 300 mg, 600 mg, and 900 mg.

2.3 Exploratory Objective

CI [redacted]

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2, open-label, dose-finding, 3-period, 3-treatment study using successively escalating doses of 300 mg, 600 mg, and 900 mg gemcabene in patients with HoFH. All patients will be on each of the successive doses for 4 weeks at a time. Patients will remain on their current stable, lipid-lowering therapy throughout the study. Patients will not be allowed in the study if they are undergoing apheresis or taking mipomersen or lomitapide.

Efficacy, PK, and safety data from this study will be used along with previously completed studies and a planned randomized, placebo-controlled study in patients with hypercholesterolemia (GEM-301) to confirm the appropriate dose of gemcabene for use in Phase 3 studies. An effective dose is defined as a dose that achieves ≥15% mean reduction in LDL-C after 4 weeks of treatment with the study totaling 12 weeks of treatment.

Approximately 8 patients will be enrolled into the study. Total study duration will be up to 18 weeks and will consist of a Screening Visit, a Treatment Period, and a Follow-up Visit.

The Screening Visit will occur up to 14 days prior to Day 1. Patients will sign the informed consent form (ICF) prior to any study procedures being performed. Patients must meet all of the inclusion and none of the exclusion criteria to be eligible for study participation.

The Treatment Period is a sequential design whereby each patient will receive gemcabene 300 mg QD for 4 weeks. The same patients will then receive a 600 mg dose QD for 4 weeks and finally 900 mg dose QD for 4 weeks. There will be no interruptions in gemcabene dosing when changing from the 300 mg to the 600 mg dose or when changing from the 600 mg to the 900 mg dose unless there are clinically significant safety issues resulting in the temporary or permanent discontinuation of study drug. The first 300 mg dose of study drug will be administered at the site on Day 1. For days when patients will self-dose, they will be instructed to take study drug at the same time each morning on an empty stomach 30 to 60 minutes prior to breakfast. For patients also taking bile acid sequestrants, study drug should be taken at least 2 hours before administration of bile acid sequestrants. Assessments will be performed after the patient has been on the study drug for 2 weeks for each dosing level and on the last day of each dose.

For each escalated dose, percent change from baseline in LDL-C will be calculated using the baseline LDL-C value and the final LDL-C value measured for each dose. Baseline will be defined as the average of the Screening Visit occurring up to 14 days prior to Day 1 and Day 1 (pre-dose) measurements.

Pharmacokinetic samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose) and 0.5, 1, 2, 3, 5, and 12 hours post-dose on Day 28, Day 56, and Day 84 in collection tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) as the anticoagulant; for determination of gemcabene repeat-dose PK parameters, steady state is assumed following QD administration for 28 days and therefore, plasma gemcabene concentrations at 24 hours post-dose are considered to be equal to pre-dose concentrations. For all other study visits where routine plasma drug monitoring will be performed (Day 1, Day 14, Day 42, Day 70, and the Early Termination [ET] Visit, if applicable), samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose if a previous day's dose occurred).

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, specifically patients with HoFH.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

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

1. Provision of written and signed informed consent (by patient or legal guardian) prior to any study-specific procedure;
2. Male or female ≥17 years of age at time of consent;
3. Diagnosis of HoFH by genetic confirmation (including compound heterozygosity) or a clinical diagnosis based on either (1) a history of an untreated LDL-C concentration >500 mg/dL (12.92 mmol/L) together with either appearance of xanthoma before 10 years of age, or evidence of heterozygous familial hypercholesterolemia in both parents or, if history is unavailable, (2) LDL-C >300 mg/dL (7.76 mmol/L) on maximally tolerated lipid-lowering drug therapy;
4. Currently on a stable, low-fat, low-cholesterol diet in combination with a pre-existing, regulatory-approved, not excluded lipid-lowering therapy (i.e., statins, monoclonal antibodies to PCSK9, cholesterol-absorption inhibitors, bile acid sequestrants, or nicotinic acid, or any combination thereof) at a stable dose for at least 4 weeks prior to the Screening Visit;
5. Fasting LDL-C value >130 mg/dL (3.36 mmol/L) at the Screening Visit;
6. Physical examination, including vital signs, that is within normal limits or clinically acceptable to the Investigator;
7. Weight ≥50 kg;
8. Female patients must not be pregnant or lactating. Women of child-bearing potential must have a negative serum pregnancy test at the Screening Visit and negative urine dipstick on Day 1 prior to dosing in order to qualify for the study. Women who are surgically sterile or are clinically confirmed to be post-menopausal (i.e., documented amenorrhea for ≥1 year in the absence of other biological or physiological causes) are not considered to be of child-bearing potential; and
9. Women of child-bearing potential must agree to use acceptable methods of contraception throughout the duration of the study and for 30 days after the last dose of study drug. For this study, double-barrier contraception is required.

4.2 Exclusion Criteria

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

1. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolemia (e.g., nephrotic syndrome or hypothyroidism);
2. Abnormal liver function test at 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). Patients 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;

3. Moderate (Grade B) or severe (Grade C) chronic hepatic impairment according to the Child-Pugh classification;
4. Active liver disease (e.g., cirrhosis, alcoholic liver disease, hepatitis B virus [HBV], hepatitis C virus [HCV], autoimmune hepatitis, liver failure, liver cancer), history of liver transplant, or known diagnosis of human immunodeficiency virus (HIV);
5. Triglycerides value >400 mg/dL (4.52 mmol/L) at the Screening Visit;
6. Moderate to severe renal insufficiency defined as an estimated GFR <30 mL/min/1.73 m^2 (calculated using The Chronic Kidney Disease Epidemiology Collaboration equation) at the Screening Visit;
7. 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;
8. Uncontrolled thyroid disease: hyperthyroidism or hypothyroidism as defined by thyroid-stimulating hormone (TSH) below the lower limit of normal or >1.5 × ULN, respectively, at the Screening Visit. If controlled, treatment should be stable for at least 3 months prior to the Screening Visit;
9. Type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus (hemoglobin A1c [HbA1c] value >8%), or any diabetic patient taking insulin and/or thiazolidinediones;
10. New York Heart Association Class III or IV heart failure (see Appendix C);
11. 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. Patients with adequately treated stable angina, per Investigator assessment, may be included;
12. 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;
13. Uncontrolled hypertension, defined as sitting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg, and confirmed by repeat measurement;
14. Currently receiving cancer treatments or, in the Investigator's opinion, at risk of relapse for recent cancer;
15. Use of fibrate lipid-lowering agent 6 weeks prior to the Screening Visit;
16. Hypersensitivity to or a history of significant adverse reactions to any fibrate lipid-lowering agent;
17. Use of apheresis (LDL or plasma) 8 weeks prior to the Screening Visit;
18. Use of lomitapide 2 months prior to the Screening Visit;
19. Use of mipomersen 5 months prior to the Screening Visit;
20. Use of any excluded medications or supplements (e.g., potent cytochrome P450 [CYP] 3A4 inhibitors, see Appendix D);

21. 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);
22. Previously treated with gemcabene;
23. 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
24. Any other finding which, in the opinion of the Investigator, would compromise the patient's safety or participation in the study.

4.3 Withdrawal Criteria

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

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

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

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

Withdrawn patients will not be replaced unless the number of withdrawn patients study-wide is >2. If >2 patients are withdrawn from the study, then replacement patients will be enrolled to ensure ≥6 patients complete the entire study (the entire Treatment Period).

5 STUDY TREATMENTS

5.1 Treatment Groups

During the 12-week Treatment Period, all patients will receive gemcabene 300 mg QD for 4 weeks, followed by 600 mg QD for 4 weeks, followed by 900 mg QD for 4 weeks.

5.2 Rationale for Dosing

Based on the results from a completed clinical study (Study 1027-018), oral gemcabene significantly lowered LDL-C with mean percent changes of -24% and -28% at 300 mg and 900 mg, respectively, compared to -6% in the placebo group in hypercholesterolemic patients on stable statin therapy.

Gemcabene was observed to be well tolerated at single doses up to 1500 mg and multiple doses up to 900 mg. This included 837 subjects and patients 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.

5.3 Randomization and Blinding

This is an open-label study, therefore, no randomization or blinding is necessary.

5.4 Breaking the Blind

This is an open-label study, therefore, no blinding is necessary.

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/concentration	Gemcabene (parent)/tablets/300 mg
Manufacturer (drug substance)	CI [redacted]
Manufacturer (drug product)	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 CI [redacted]

Study drug will be packaged in high-density polyethylene bottles with child-resistant closures. Patients will take the following for each of the 3 dose levels:

- 300 mg: one 300 mg tablet orally QD,
- 600 mg: two 300 mg tablets orally QD, and
- 900 mg: three 300 mg tablets orally QD.

5.5.3 Study Drug Preparation and Dispensing

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

5.5.4 Study Drug Administration

Patients will be instructed to take study drug at the same time in the morning on an empty stomach 30 to 60 minutes prior to breakfast. Missed doses will be documented. For patients also taking bile acid sequestrants, study drug should be taken at least 2 hours before administration of bile acid sequestrants. If a patient misses a dose, only a single dose (and not 2 doses) should be taken on the following day.

5.5.5 Treatment Compliance

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

Compliance with administration of study drug will be assessed by means of tablet counts based on the assessment of empty bottles returned to the site at each study visit after Day 1 during the Treatment Period and the ET Visit, if applicable. Tablet counts will be recorded on the appropriate eCRF and the drug accountability log.

The Investigator or designee will remind patients at each visit of the importance of following the protocol-defined schedule for taking study drug. Reasons for not following the study drug administration schedule as described in the protocol will be clearly recorded in the source documents.

5.5.6 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 patient-by-patient basis, including specific dates and quantities. The drug accountability logs will be signed by the individual who dispenses the study drug and copies will be provided to the Sponsor.

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

Patients are required to be on a stable, low-fat, low-cholesterol diet in combination with a pre-existing, regulatory-approved, not excluded lipid-lowering therapy (i.e., statins, monoclonal antibodies to PCSK9, cholesterol-absorption inhibitors, bile acid sequestrants, or nicotinic acid, or any combination thereof) during the study.

5.6.2 Excluded Medications and/or Procedures

Patients are not permitted to receive treatment with lomitapide 2 months prior to the Screening Visit, mipomersen 5 months prior to the Screening Visit, or a fibrate lipid-lowering agent 6 weeks prior to the Screening Visit. Patients are not permitted to use strong CYP3A4 inhibitors while on the study drug. See Appendix D for a specific list of CYP3A4 inhibitors.

Additionally, plasmapheresis or LDL-apheresis is not permitted 8 weeks prior to the Screening Visit or during the study. Excluded procedures are specified in the exclusion criteria (Section 4.2).

5.6.3 Restrictions and Dietary Guidelines

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

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

Assessments that require a patient to fast will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Patients will be permitted to have water. Study drug should be taken at the same time in the morning on an empty stomach 30 to 60 minutes prior to breakfast. For patients also taking bile acid sequestrants, study drug should be taken at least 2 hours before administration of bile acid sequestrants.

Patients 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 patient concomitantly to the study, from the time of informed consent to the Follow-up Visit or the ET Visit, if applicable.

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

6 STUDY PROCEDURES

A tabular listing of the Schedule of Procedures can be found in Appendix A. Assessments that require a patient to fast will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Patients will be permitted to have water.

6.1 Informed Consent

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

6.2 Screening Visit (up to Day -14)

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

- Obtain informed consent;
- Conduct eligibility assessment based on inclusion/exclusion criteria;
- Obtain medical/surgical history and demographics;
- Perform full physical examination;
- Record vital signs, height, and weight;
- Collect urine sample for urinalysis including urine protein: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;
- 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.

6.3 Treatment Period (Visit T1 through Visit T7)

6.3.1 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 patient's health affecting eligibility;
- Record vital signs and weight;

- Collect urine sample for urinalysis including urine protein: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 and apolipoproteins;
  - hsCRP and fibrinogen;
  - CI [redacted]
  - Genetic testing for HoFH genotype; and
  - Additional samples;
- Perform 12-lead ECG pre-dose;
- Obtain PK sample pre-dose;
- 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.

6.3.2 Visit T2 (Day 14)

The following procedures will be performed at Visit T2 (Day 14 ±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; and
  - Additional samples;
- Perform 12-lead ECG pre-dose;
- Obtain PK sample pre-dose (must be 24 ±2 hours after previous day's dose);
- Administer study drug;
- Assess and document study drug compliance;
- Dispense study drug and instructions;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent); and

- Assess adverse events and update concomitant medications.

6.3.3 Visit T3 (Day 28)

The following procedures will be performed at Visit T3 (Day 28 ±3 days):

- Perform symptom-directed physical examination;
- Record vital signs and weight;
- Collect urine sample for urinalysis including urine protein: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 and apolipoproteins;
  - hsCRP and fibrinogen; and
  - Additional samples;
- Perform 12-lead ECG pre-dose and 2 hours post-dose;
- Obtain PK sample pre-dose (must be 24 ±2 hours after previous day's dose) and 0.5, 1, 2, 3, 5, and 12 hours post-dose. The window for PK samples obtained at time intervals <24 hours will be ±10 minutes;
- Administer study drug;
- Assess and document study drug compliance;
- Dispense study drug and instructions;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent); and
- Assess adverse events and update concomitant medications.

6.3.4 Visit T4 (Day 42)

The following procedures will be performed at Visit T4 (Day 42 ±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; and
  - Additional samples;
- Perform 12-lead ECG pre-dose;

- Obtain PK sample pre-dose (must be 24 ±2 hours after previous day's dose);
- Administer study drug;
- Assess and document study drug compliance;
- Dispense study drug and instructions;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent); and
- Assess adverse events and update concomitant medications.

6.3.5 Visit T5 (Day 56)

The following procedures will be performed at Visit T5 (Day 56 ±3 days):

- Perform symptom-directed physical examination;
- Record vital signs and weight;
- Collect urine sample for urinalysis including urine protein: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 and apolipoproteins;
  - hsCRP and fibrinogen; and
  - Additional samples;
- Perform 12-lead ECG pre-dose and 2 hours post-dose;
- Obtain PK sample pre-dose (must be 24 ±2 hours after previous day's dose) and 0.5, 1, 2, 3, 5, and 12 hours post-dose. The window for PK samples obtained at time intervals <24 hours will be ±10 minutes;
- Administer study drug;
- Assess and document study drug compliance;
- Dispense study drug and instructions;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent); and
- Assess adverse events and update concomitant medications.

6.3.6 Visit T6 (Day 70)

The following procedures will be performed at Visit T6 (Day 70 ±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; and
  - Additional samples;
- Perform 12-lead ECG pre-dose;
- Obtain PK sample pre-dose (must be 24 ±2 hours after previous day's dose);
- Administer study drug;
- Assess and document study drug compliance;
- Dispense study drug and instructions;
- Explain dietary instructions (counsel per NCEP ATP-III guidelines or equivalent); and
- Assess adverse events and update concomitant medications.

6.3.7 Visit T7 (Day 84)

The following procedures will be performed at Visit T7 (Day 84 [can be performed up to 3 days prior to Day 84, but not after Day 84]):

- Perform full physical examination;
- Record vital signs and weight;
- Collect urine sample for urinalysis including urine protein: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 Day 84 will also be followed-up 2 weeks (±3 days) after the last dose of study drug in addition to the 4 week (±3 days) Follow-up Visit), coagulation, and hematology;
  - Fasting lipid panel and apolipoproteins;
  - hsCRP and fibrinogen;
  - Cl and
  - Additional samples;
- Perform 12-lead ECG pre-dose and 2 hours post-dose;
- Obtain PK sample pre-dose (must be 24 ±2 hours after previous day's dose) and 0.5, 1, 2, 3, 5, and 12 hours post-dose. The window for PK samples obtained at time intervals <24 hours will be ±10 minutes;
- Administer study drug;
- Assess and document study drug compliance; and
- Assess adverse events and update concomitant medications.

6.4 Follow-up Visit (Day 112)

The Follow-up Visit will be conducted as a telephone call 4 weeks (±3 days) after the last dose of study drug, unless the patient requires a site visit due to an abnormal result at Day 84 (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 112 ±3 days):

- Perform symptom-directed physical examination (only for patients who had an abnormal result at Day 84 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event);
- Collect urine sample for urinalysis including urine protein:creatinine ratio and NGAL (only for patients who had an abnormal result at Day 84 [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 patients who had an abnormal result at Day 84 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event); and
- Assess adverse events and update concomitant medications.

6.5 Early Termination Visit and Withdrawal Procedures

For patients 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 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 and apolipoproteins;
  - hsCRP and fibrinogen;
  - CI and
  - Additional samples;
- Perform 12-lead ECG;
- Obtain PK sample (must be 24 ±2 hours after previous day's dose);
- Assess and document study drug compliance; and
- Assess adverse events and update concomitant medications.

7 EFFICACY ANALYSES

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, Day 14, Day 28, Day 42, Day 56, Day 70, and Day 84 (or the ET Visit, if applicable);
- Fasting ApoB, ApoA-I, ApoA-II, ApoC-II, ApoC-III, ApoE, and lipoprotein(a) (Lp[a]) at baseline, Day 28, Day 56, and Day 84 (or the ET Visit, if applicable);
- hsCRP at baseline, Day 28, Day 56, and Day 84 (or the ET Visit, if applicable);
- Fibrinogen at baseline, Day 28, Day 56, and Day 84 (or the ET Visit, if applicable); and
- CI [redacted]

8 PHARMACOKINETIC ASSESSMENTS

The PK assessments of this study are to evaluate the gemcabene systemic exposure on Day 28, Day 56, and Day 84 and perform routine plasma drug monitoring on Day 1, Day 14, Day 42, and Day 70.

The actual PK blood sampling times will be captured on the eCRF. The actual dosing time on PK sampling days and days preceding sampling will also be captured on the eCRF.

Pharmacokinetic samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose) and 0.5, 1, 2, 3, 5, and 12 hours post-dose on Day 28, Day 56, and Day 84 in collection tubes containing K_2EDTA as the anticoagulant; for determination of gemcabene repeat-dose PK parameters, steady state is assumed following QD administration for 28 days and therefore, plasma gemcabene concentrations at 24 hours post-dose are considered to be equal to pre-dose concentrations. For all other study visits where routine plasma drug monitoring will be performed (Day 1, Day 14, Day 42, Day 70, and the ET Visit, if applicable), samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose if a previous day's dose occurred).

The window for PK samples obtained at time intervals <24 hours will be ±10 minutes and the window for samples obtained at 24 hours will be ±2 hours.

9 SAFETY ASSESSMENTS

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate 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). Patients should be instructed to report any adverse event that they experience to the Investigator. Beginning with the signing of the informed consent until the time of the first dose of study drug (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 patient 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 patient 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.

9.1.1 Adverse (Drug) Reaction

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

9.1.2 Unexpected Adverse Drug Reaction

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

9.1.3 Assessment of Adverse Events by the Investigator

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

Assessment of Severity:

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

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

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

Causality Assessment:

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

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

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

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

The following factors should also be considered:

- The temporal sequence from study drug administration -
    - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant diseases (medical history) -
    - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug -
  - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug -
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses -
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug -
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

9.1.4 Specific Safety Measures

9.1.4.1 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 patient's past medical history, concomitant medications (including over the counter drugs and herbal supplements), and any recent symptoms (e.g., bleeding, shortness of breath, fatigue) will be reviewed to determine a potential etiology and make a clinical assessment of the significance of the finding.

9.1.4.2 Creatinine increase

If, at any visit, a creatinine increase of >0.3 mg/dL (27 µmol/L) from baseline or a GFR decrease of >15 mL/min from baseline is observed, repeat chemistry will be performed. The patient's past medical history, concomitant medications (including over the counter drugs and herbal supplements), and any recent symptoms (e.g., fatigue, malaise, polyuria/oliguria, or palpitations) will be reviewed to determine a potential etiology and make a clinical assessment of the significance of the finding.

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

9.1.4.3 Possible muscle and liver injury

For muscle injury, creatine kinase (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.

9.2 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 patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations;
  - NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.
  - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency or drug abuse.

9.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to PI Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, PI Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to PI Safety at

PI or call the PI SAE hotline (telephone number listed below), and fax the completed paper SAE form to PI (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: PI Clinical Safety
PI

PI

Follow-up Reports

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

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to PI Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

9.4 Pregnancy Reporting

If a patient participating in the study becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to PI Clinical Safety within 24 hours of being notified. PI Clinical Safety will then forward the Exposure *In Utero* form to the Investigator for completion.

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

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

9.5 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 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 will not be necessary. Listings of cases related to these NIMPs will be included in the Development Safety Update Report.

9.6 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 patient to fast will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Patients will be permitted to have water.

Central laboratory results will be provided to the sites. Laboratory results that appear potentially spurious based on the Investigator's clinical assessment and review of the patient's medical history may be repeated for confirmation of the finding. Reassessments of non-qualifying screening labs must be reviewed and approved by the 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 patients who had an abnormal result at Day 84 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event). Clinically significant abnormal creatinine results at Day 84 (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 and description of when repeat or reflexive testing will be required.

A fasting lipid panel will be assessed at all study visits, excluding the Follow-up Visit. Fasting apolipoproteins, hsCRP, and fibrinogen will be assessed at Day 1, Day 28, Day 56, Day 84, and the ET Visit, if applicable. In addition to these lipid parameters, CI [redacted] will also be measured at Day 1, Day 84, and the ET Visit, if applicable.

A urine sample for urinalysis will be collected at all study visits and the Follow-up Visit (only for patients who had an abnormal result at Day 84 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event). A urine microscopic examination will be performed when the dipstick result is abnormal (positive for blood, leukocyte esterase, or nitrites). Urine protein:creatinine ratio will be performed at the Screening Visit, Day 1, Day 28, Day 56, Day 84, the Follow-up Visit (only for patients who had an abnormal result at Day 84 [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, Day 28, Day 56, Day 84, the Follow-up Visit (only for patients who had an abnormal result at Day 84 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event), and the ET Visit, if applicable.

Serology tests for HBV, HCV, and HIV will be conducted at the Screening Visit.

For women of child-bearing potential only, a serum pregnancy test will be conducted at the Screening Visit, Day 84, and the ET Visit, if applicable. A urine pregnancy test will be conducted at all other study visits, excluding the Follow-up Visit.

Thyroid-stimulating hormone and HbA1c will be measured at the Screening Visit.

9.7 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 patient has rested comfortably for at least 5 minutes. Blood pressure at the Screening Visit should be obtained in both arms and the arm with the highest value should be used for ongoing monitoring throughout the rest of the study. If an automated assessment is performed, the same machine should be used for the patient throughout the study when possible. Care should be taken to ensure an appropriate cuff size is utilized.

9.8 Electrocardiograms

Electrocardiograms will be performed in triplicate and sent to a central reviewer. Patients should be lying quietly in a fully supine position for at least 10 minutes prior to each 12-lead ECG. A 12-lead ECG will be performed at the Screening Visit and pre-dose on Day 1, Day 14, Day 42, Day 70, and the ET Visit, if applicable. Electrocardiograms will be performed pre-dose and 2 hours post-dose on Day 28, Day 56, and Day 84.

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 tracings will be kept as source data.

9.9 Physical Examinations

A full physical examination will be performed at the Screening Visit, Day 84, and the ET Visit, if applicable, and includes genitourinary examination per the Investigator's discretion and does not include a rectal examination. Assessment for xanthoma or arcus should also be part of the full physical examination. Any changes or improvements in xanthoma or arcus will be captured on the appropriate eCRF.

A symptom-directed physical examination will be conducted at all other study visits and the Follow-up Visit (only for patients who had an abnormal result at Day 84 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event).

Height will be measured at the Screening Visit and weight will be measured at all study visits, excluding the Follow-up Visit.

9.10 Medical/Surgical History and Demographics

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

9.11 Genetic Testing

Peripheral blood cell DNA for determination of genetic testing for the HoFH genotype mutational status will be collected at Day 1 for all patients.

This data will be used to confirm diagnosis, categorize receptor function according to published data, and possibly show responses for receptor negative patients (if enrolled) separately from those with at least one defective receptor.

9.12 Additional Samples

Additional blood samples will be collected at all study visits during the Treatment Period and the ET Visit, if applicable, to be available for analysis of exploratory biomarkers associated with lipid metabolism, repeat lipid testing, blood drug levels, and/or repeat or additional clinical laboratory and urine testing in the event of a safety issue.

10 STATISTICS

10.1 Analysis Populations

Two analysis populations are designed for the study: the Intent-to-Treat (ITT) Population and the Safety Population. The Safety Population will include all patients who are enrolled into the study and have at least 1 dose of study drug, while the ITT Population will include patients from the Safety Population who also have a post-baseline efficacy assessment.

10.2 Statistical Methods

10.2.1 Analysis of Efficacy

Given the proposed crossover design of this study, a within-patient analysis can be performed for the comparison of dose groups. For continuous variables, the dose groups will be compared on their change and percent reduction from baseline (using their pre-treatment baseline value). A longitudinal analysis will be performed with a mixed-effects model repeated measures analysis including percent change in LDL-C as the dependent variable, visit as a fixed effect and patient as a random effect. The additional drug benefit with increasing dose will be estimated from the mixed-effects model. Least-squares mean differences and corresponding 95% confidence intervals, separately for each of the 3 paired comparisons (300 versus 600 mg, 300 versus 900 mg, and 600 versus 900 mg) will be provided. In addition, a scatterplot with regression curve fit of the percent reduction from baseline versus dose will be performed. For binary variables such as the percentage of patients, descriptive statistics will be calculated for each dose group.

Baseline will be defined as the average of the Screening Visit occurring up to 14 days prior to Day 1 and Day 1 (pre-dose) measurements.

10.2.1.1 Primary efficacy analysis

The primary efficacy analysis is the percent change in LDL-C from baseline to Day 28, Day 56, and Day 84.

10.2.1.2 Secondary efficacy analyses

The secondary efficacy analyses are the following:

- The change in LDL-C from baseline to Day 28, Day 56, and Day 84;
- The change and percent change in lipid parameters (non-HDL-C, TC, TG, HDL-C, and VLDL-C) from baseline to Day 28, Day 56, and Day 84;
- The change and percent change in lipid parameters (non-HDL-C, TC, TG, HDL-C, and VLDL-C) from baseline to Day 28, Day 56, and Day 84 according to the receptor mutation status;
- The number (%) of patients achieving LDL-C reduction of ≥15%, ≥20%, ≥25%, and ≥30% at Day 28, Day 56, and Day 84;
- The number (%) of patients achieving an LDL-C value <100 mg/dL (2.59 mmol/L) at Day 28, Day 56, Day 84, and at any time during the study;
- The change and percent change in ApoB, ApoA-I, ApoA-II, ApoC-II, ApoC-III, ApoE, and Lp(a) from baseline to Day 28, Day 56, and Day 84;

- The change and percent change in hsCRP from baseline to Day 28, Day 56, and Day 84; and
- The change and percent change in fibrinogen from baseline to Day 28, Day 56, and Day 84.

10.2.1.3 Exploratory analysis

CI [redacted]

10.2.1.4 Pharmacokinetic analysis

The PK assessments of this study are to evaluate the gemcabene systemic exposure on Day 28, Day 56, and Day 84 and perform routine plasma drug monitoring on Day 1, Day 14, Day 42, and Day 70.

The actual PK blood sampling times will be captured on the eCRF. The actual dosing time on PK sampling days and days preceding sampling will also be captured on the eCRF.

Pharmacokinetic samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose) and 0.5, 1, 2, 3, 5, and 12 hours post-dose on Day 28, Day 56, and Day 84 in collection tubes containing K_2EDTA as the anticoagulant; for determination of gemcabene repeat-dose PK parameters, steady state is assumed following QD administration for 28 days and therefore, plasma gemcabene concentrations at 24 hours post-dose are considered to be equal to pre-dose concentrations. For all other study visits where routine plasma drug monitoring will be performed (Day 1, Day 14, Day 42, Day 70, and the ET Visit, if applicable), samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose if a previous day's dose occurred).

The window for PK samples obtained at time intervals <24 hours will be ±10 minutes and the window for samples obtained at 24 hours will be ±2 hours.

The following PK parameters will be calculated, as appropriate, from the individual plasma concentrations of gemcabene using a non-compartmental approach. Pharmacokinetic variables will be computed using WinNonlin Professional® or other appropriate software.

- C_{max}: maximum plasma concentration,
- t_{max} (h): time to maximum plasma concentration,
- AUC_{0-t} (ng·h/mL): area under the concentration-time curve to the last quantifiable time, and
- AUC_{0-24} (ng·h/mL): area under the concentration-time curve to the 24-hour time point.

10.2.2 Missing Data

The primary analyses of the primary and secondary outcome variables will use linear mixed effects models. This analysis method will allow for inclusion of patients with missing values thus using the maximum amount of data for the analysis and making fewer assumptions about the missing data compared to a more traditional per protocol analysis.

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

repeat measurements will be recorded in the clinical database. In listings and narratives, all laboratory values including unscheduled and repeat values will be included.

10.2.3 Analysis of Safety

Safety will be assessed using the population of all patients who receive any amount of study drug. The assessment of safety will include adverse events, clinical laboratory assessments, ECGs, physical examinations, and vital signs. The safety analysis will be based primarily on the frequency of new or worsening adverse events, laboratory abnormalities, and SAEs. Other safety data will be summarized as appropriate.

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

Safety laboratory data will be summarized at baseline, Day 28, Day 56, and Day 84, and change from baseline to Day 28, Day 56, and Day 84. Frequency counts of new or worsening abnormalities will also be provided.

10.2.4 Sample Size Determination

The primary goal of the study is to assess the mean percent change in LDL-C from baseline over 12 weeks of treatment from the 3 dose levels. Dosing 8 patients per group will yield reasonable precision in estimation in mean change from baseline in LDL-C.

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 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.

11.1.2 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).

11.1.3 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.

11.1.4 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.

11.1.5 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.

11.2 Record Keeping

Records of patients, 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.

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

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

12.2 Institutional Review Board/Ethics Committee

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

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

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

12.3 Informed Consent

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

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

12.4 Patient Card

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

12.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, Directive 2001/20/EC, and applicable regulatory requirements (e.g., 21 CFR 312 Part D), 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 patients 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 patient 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.

12.6 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. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

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

12.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (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.

12.8 Publication Policy

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

12.9 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.

12.10 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.

12.11 Legal Aspects

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

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

12.12 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.

12.13 Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of 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 patients within 2 weeks. As directed by Gemphire, all study materials must be collected and all eCRFs completed to the greatest extent possible.

13 STUDY ADMINISTRATIVE INFORMATION

13.1 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 patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

13.2 Address List

13.2.1 Sponsor

Gemphire Therapeutics Inc.
43334 Seven Mile Road, Suite 1000
Northville, Michigan 48167
Telephone: +1-248-681-9815
Facsimile: +1-734-864-5765

13.2.2 Contract Research Organization

PI

14 REFERENCES

1. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. 2014;35(32):2146-2157.
2. Bisgaier and Auerbach, 2015. Gemcabene and atorvastatin alone and combined markedly reduce LDL-C in LDL receptor-deficient mice, a model of Homozygous Familial Hypercholesterolemia. Circulation. 2015; 132: A17824.
3. Sexton KE, Lee HT, Massa M, et al. Inhibitors of lipoprotein(a) assembly. Bioorg Med Chem. 2003;11(22):4827-45.
4. Stein EA. Low-density lipoprotein cholesterol reduction by inhibition of PCSK9. Curr Opin Lipidol. 2013;24(6):510-7.
5. Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015;36(36):2425-37.

APPENDIX A: SCHEDULE OF PROCEDURES

	Screening	Treatment Period[a]							Follow-up[b]	ET
		300 mg Gemcabene			600 mg Gemcabene		900 mg Gemcabene			
	up to Day -14	Day 1[c]	Day 14	Day 28	Day 42	Day 56	Day 70	Day 84	Day 112	
	Visit S1	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5	Visit T6	Visit T7		
Informed consent	X									
Inclusion/exclusion criteria	X									
Medical/surgical history and demographics	X									
Full physical examination[d]	X							X		X
Symptom-directed physical examination		X	X	X	X	X	X		X[e]	
Vital signs[f], height[g], and weight	X	X	X	X	X	X	X	X		X
Urinalysis[h]	X	X	X	X	X	X	X	X	X[e]	X
Serum/urine pregnancy test[i]	X	X	X	X	X	X	X	X		X
Safety chemistry panel, coagulation, and hematology[j]	X	X	X	X	X	X	X	X	X[e]	X
TSH, HbA1c, and serology[k]	X									
Fasting lipid panel[l]	X	X	X	X	X	X	X	X		X
Fasting apolipoproteins[m]		X		X		X		X		X
hsCRP and fibrinogen		X		X		X		X		X
CI [redacted]		X						X		X
Study drug administration		X	X	X	X	X	X	X		
Dispense study drug and instructions		X	X	X	X	X	X			
Compliance check			X	X	X	X	X	X		X
Dietary instructions[n]	X	X	X	X	X	X	X			
PK sampling[o]		X	X	X	X	X	X	X		X
12-lead ECG[p]	X	X	X	X	X	X	X	X		X
Adverse events	X[q]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Genetic testing		X								
Additional samples		X	X	X	X	X	X	X		X

Footnotes appear on the following page

a. Study assessments will be completed ±3 days of given time point for all study visits from Day 1 through Day 70. Day 84 assessments can be performed up to 3 days prior to Day 84, but not after Day 84.
b. The Follow-up Visit will be conducted as a telephone call 4 weeks (±3 days) after the last dose of study drug, unless the patient requires a site visit due to an abnormal result at Day 84 (or the ET Visit, if applicable) or an ongoing treatment-related adverse event.
c. Procedures will be performed pre-dose. The Investigator will inquire with the patient at Day 1 to determine if there have been any changes in the patient's health affecting eligibility or requiring an update to their medical and surgical history.
d. A full physical examination includes genitourinary examination per the Investigator's discretion and does not include a rectal examination. Assessment for xanthoma or arcus should also be part of the full physical examination. Any changes or improvements in xanthoma or arcus will be captured on the appropriate eCRF.
e. Only for patients who had an abnormal result at Day 84 (or the ET Visit, if applicable) or an ongoing treatment-related adverse event.
f. Vital signs include pulse rate, blood pressure, respiration rate, and temperature. Blood pressure should be obtained in the seated position, after the patient has rested comfortably for at least 5 minutes. Blood pressure at the Screening Visit should be obtained in both arms and the arm with the highest value should be used for ongoing monitoring throughout the rest of the study. If an automated assessment is performed, the same machine should be used for the patient throughout the study when possible. Care should be taken to ensure an appropriate cuff size is utilized.
g. Height will be measured only at the Screening Visit.
h. A urine microscopic examination will be performed when the dipstick result is abnormal (positive for blood, leukocyte esterase, or nitrites). Urine protein:creatinine ratio will be performed at the Screening Visit, Day 1, Day 28, Day 56, Day 84, the Follow-up Visit (only for patients who had an abnormal result at Day 84 [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, Day 28, Day 84, the Follow-up Visit (only for patients who had an abnormal result at Day 84 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event), and the ET Visit, if applicable.
i. For women of child-bearing potential only, a serum pregnancy test will be conducted at the Screening Visit, Day 84, and the ET Visit, if applicable. A urine pregnancy test will be conducted at all other study visits, excluding the Follow-up Visit.
j. Clinically significant abnormal creatinine results at Day 84 (or the ET Visit, if applicable) will also be followed-up 2 weeks (±3 days) after the last dose of study drug in addition to the 4 week (±3 days) Follow-up Visit. See Appendix B for a list of analytes and description of when repeat or reflexive testing will be required.
k. Serology includes HBV, HCV, and HIV.
l. 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. Patients will be permitted to have water.
m. Includes ApoB, ApoA-I, ApoA-II, ApoC-II, ApoC-III, ApoE, and Lp(a). Fasting will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Patients will be permitted to have water.
n. Patients will be counseled on a low-fat, low-cholesterol diet (NCEP ATP-III guidelines or equivalent).
o. Pharmacokinetic samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose) and 0.5, 1, 2, 3, 5, and 12 hours post-dose on Day 28, Day 56, and Day 84 in collection tubes containing K_2EDTA as the anticoagulant. For all other study visits where routine plasma drug monitoring will be performed (Day 1, Day 14, Day 42, Day 70, and the ET Visit, if applicable), samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose if a previous day's dose occurred). The window for PK samples obtained at time intervals <24 hours will be ±10 minutes.
p. Electrocardiograms will be performed in triplicate and sent to a central reviewer. A 12-lead ECG will be performed at the Screening Visit and pre-dose on Day 1, Day 14, Day 42, Day 70, and the ET Visit, if applicable. Electrocardiograms will be performed pre-dose and 2 hours post-dose on Day 28, Day 56, and Day 84. Patients should be lying quietly in a fully supine position for at least 10 minutes prior to each 12-lead ECG.
q. Serious adverse events that occur prior to the first dose of study drug (Day 1) should be reported as an update to medical history as well as be reported on the appropriate adverse event eCRF.

Apo = apolipoprotein; ECG = electrocardiogram; eCRF = electronic Case Report Form; ET = Early Termination; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; K_2EDTA = dipotassium ethylenediaminetetraacetic acid; 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; CI [redacted] CI [redacted] PK = pharmacokinetic; 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

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 (NGAL) [3]

1. A urine microscopic examination will be performed when dipstick results are abnormal (positive for blood, leukocyte esterase, or nitrites).
2. Urine protein:creatinine ratio will be performed at the Screening Visit, Day 1, Day 28, Day 56, Day 84, the Follow-up Visit (only for patients who had an abnormal result at Day 84 [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, Day 28, Day 56, Day 84, the Follow-up Visit (only for patients who had an abnormal result at Day 84 [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 patients of child-bearing potential.

Serology

Hepatitis B	Hepatitis C
Human Immunodeficiency Virus	

Coagulation

Prothrombin time	Activated partial thromboplastin time
International normalized ratio	

Genetic Testing

Homozygous familial hypercholesterolemia genotyping

Efficacy Parameters

The following efficacy parameters will be assessed in this study:

Apolipoprotein (Apo) A-I	ApoA-II
ApoB	ApoC-II
ApoC-III	ApoE
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	Lipoprotein(a)
CCI	Fibrinogen

APPENDIX C: NEW YORK HEART ASSOCIATION CONGESTIVE HEART FAILURE CLASSIFICATION

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

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

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

- Patients with new or unexplained muscle symptoms should have an unscheduled visit scheduled within 7 days of site notification. At this visit, samples should be sent for a full chemistry panel, including CK, liver, and renal function.
- Patients with CK elevations of >3 × upper limit of normal (ULN) who are asymptomatic should be considered for an unscheduled visit (+ isozymes), based upon medical judgment.
- All patients with CK elevations >10 × ULN should have an unscheduled visit (+ isozymes). 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 patients are instructed to not undertake any form of strenuous physical activity for at least 24 hours prior to repeat blood testing.

Hepatic Monitoring

Patients with hepatic enzyme elevations should be managed according to the standard of care, at the discretion of the Investigator. For patients with signs or symptoms suggestive of hepatitis, an unscheduled visit and a chemistry panel should be performed. Patients with an alanine aminotransferase (ALT) >2 × ULN with symptoms suggestive of hepatitis should have an unscheduled visit. Patients 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 patient 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.

Recommended Hepatic Discontinuation Criteria

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%).

If patients are receiving statins in addition to study treatment, 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.