Protocol	
Official title:	A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 in Patients With Heterozygous Familial Hypercholesterolemia
NCT Number:	NCT03038022
Document Date:	14 November 2016

CLINICAL STUDY PROTOCOL

A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 in Patients With Heterozygous Familial Hypercholesterolemia

Investigational Product: MGL-3196

Protocol Number: MGL-3196-06

Sponsor:

Madrigal Pharmaceuticals, Inc.

Four Tower Bridge, 200 Barr Harbor Drive, Suite 400

West Conshohocken, PA 19428

USA

Telephone: 610-220-7260

Version Number: 2.0

Date: 14 November 2016

Original Protocol: 12 July 2016

Amendment 1: 14 November 2016

SIGNATURE PAGE

STUDY TITLE: A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 in Patients With Heterozygous Familial Hypercholesterolemia

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

Signature	Date
[redacted]	
[redacted]	
[redacted]	

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. 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 Madrigal Pharmaceuticals, 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 Madrigal Pharmaceuticals, 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 Madrigal Pharmaceuticals, 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, IRB/IEC regulations and International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SUMMARY OF PROTOCOL AMENDMENT CHANGES

Changes that have the potential to affect either the efficacy or safety assessments:

Treatment groups changed from placebo, 80, and 120 mg to placebo and 100 mg / 60 mg groups. (Synopsis and Sections 2.1, 3.1, 5.1, 5.3, 10.2.1.1, and 10.2.4).

Patients instructed to take statins or other lipid lowering therapy at night at least 2 weeks before randomization, and will to continue this practice for the duration of the study. (Synopsis and Section 3.1).

Patients randomized to MGL-3196 100 mg will receive MGL-3196 60 mg between the week 2 and 4 visits, while patients receiving placebo will continue to receive placebo. (Synopsis and Section 3.1 and 5.1).

At Week 2, added 4-hr post dose PK sample collection for dose determination (Synopsis and Sections 3.1, 6.4.2, and 8 and Appendix A).

Possible dose reduction at Week 4 will be based Week 2 postdose MGL-3196 blood levels. If MGL-3196 blood level < 1,500 ng/mL patient be placed on MGL-3196 100 mg, while patients with MGL-3196 blood levels ≥ 1,500 ng/mL will continue to receive 60 mg. (Synopsis and Sections 3.1, and 5.1).

Added Secondary Objective of percent change from baseline in LDL-C and effective of exposure to MGL-3196 on LDL-C lowering (Synopsis, Sections 2.2, and 7).

[redacted]

Added Exclusion Criteria #9 – Thyroid replacement therapy (Synopsis and Section 4.2).

Exclusion Criteria #10 – updated note regarding hypothyroidism (Synopsis and Section 4.2).

Exclusion Criteria #15 – change eGFR rate from < 40 to < 60 (Synopsis and Section 4.2).

Added that bile acid sequestrants should be take them approximately 4-6 hours after taking their MGL-3196 study drug or matching placebo and approximately 4-6 hours prior to their evening statin dose. (Section 5.6.2)

Added at screen to verify that patient is on stable maximally tolerated dose of atorvastatin or rosuvastatin (up to 20 mg) and adjust statin dosing to once daily in evenings (Section 6.2).

At screening no assessment of TBG or ApoCIII (Sections 6.2 and 9.8).

Added that patients should arrive at the clinic in the morning after at least 10 hours of fasting, and record the time of their statin dose from the night before. (Section 6.4)

Collect backup sample at Baseline and Week 12 Visit (Sections 6.4.1, 6.4.5, and 9.8).

Pre-dose PK for measurement of statin level. (Sections 6.4.1 and 8).

Removal of the pre-dose 12-Lead ECG at Week 2 Visit. (Sections 6.4.2 and 9.10).

Perform 12-Lead ECG at 4 hours post dose (Sections 6.4.2 and 9.10).

PK assessment at predose and 4 h postdose for statins and MGL-3196. (Sections 6.4.2 and 8).

Added dispensing of study drug at Week 2 Visit. (Section 6.4.2).

Removal of the 2-5 hour post dose PK sample at Week 4. (Section 6.4.3).

Added Section 9.13 – Drug Inducted Liver Injury Monitoring.

Removed DSMB meeting that would occur after at least 50 patients across Studies MGL-3196-05 and MGL-3196-06 had been exposed to MGL-3196 for 6 weeks. (Synopsis and Sections 3.1 and 10.2.3).

Administrative changes not affecting the content or conduct of the protocol:

Updates to the Introduction (Section 1).

Changes to references corresponding to changes in the Introduction (14).

Change in title for [redacted] (Signature Page).

Change to Sponsor address (Cover Page and Section 13.2.1).

Added address for [redacted] central laboratory in Belgium (Section 13.2.4)

SYNOPSIS

TITLE: A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 in Patients With Heterozygous Familial Hypercholesterolemia

PROTOCOL NUMBER: MGL-3196-06

INVESTIGATIONAL PRODUCT: MGL-3196

PHASE: 2

INDICATION: Heterozygous familial hypercholesterolemia (HeFH)

OBJECTIVES:

The primary objective of this study is to determine the effect of each of two separate treatment groups (the "100 mg group" and the "60 mg group") of once-daily oral dose of MGL-3196 and matching placebo on the percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in patients with HeFH.

The secondary objectives of this study are the following:

- To evaluate the safety profile, including any changes in thyroid axis hormones, and tolerability of once-daily oral dosing regimen of MGL-3196 versus placebo after 12 weeks in patients with HeFH;
- To determine the effect of once-daily oral dosing regimen of MGL-3196 versus placebo for 12 weeks on the percent change from baseline on the following assessments in patients with HeFH:
  - Non-high-density lipoprotein cholesterol (non-HDL-C),
  - Apolipoprotein B (ApoB),
  - Total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio,
  - Triglycerides,
  - Lipoprotein(a),
  - Apolipoprotein A1 (ApoA1)/ApoB ratio, and
  - Lipoprotein particle assessment; and
- To determine the effect of once-daily oral dose of MGL-3196 versus placebo for 12 weeks on the absolute change from baseline in LDL-C in patients with HeFH.
- To determine the effect of all patients (100 and 60 mg groups) on per cent change from baseline in LDL-C
- To determine the effect of exposure to MGL-3196 on LDL-C lowering

POPULATION:

The population for this study is male and female patients ≥18 years of age who have met the diagnostic criteria for HeFH outlined by the Simon Broome Register Group (Appendix C) or World Health Organization (WHO)/Dutch Lipid Network (score >8; Appendix D).

Inclusion Criteria:

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

1. Must be willing to participate in the study and provide written informed consent;
2. Male and female adults ≥18 years of age;
3. Female patients of child bearing potential with negative serum pregnancy (beta human chorionic gonadotropin) test who are not breastfeeding, do not plan to become pregnant during the study, and agree to use effective birth control (ie, condoms, diaphragm, non-hormonal intrauterine device [IUD], or sexual abstinence [only if this is in line with the patient's current lifestyle]) throughout the study and for at least 1 month after study completion; hormonal contraception (estrogens stable ≥3 months) and hormonal IUDs are permitted if used with a secondary birth control measure (eg, condoms); OR female patients of non-child bearing potential (ie, surgically [bilateral oophorectomy, hysterectomy, or tubal ligation] or naturally sterile [>12 consecutive months without menses]); male patients who have sexual intercourse with a female partner of child bearing potential from the first dose of study drug until 1 month after study completion must either be surgically sterile (confirmed by documented azoospermia >90 days after the procedure) OR agree to use a condom with spermicide. All male patients must agree not to donate sperm from the first dose of study drug until 1 month after study completion;
4. Must have a diagnosis of HeFH by genetic testing or by having met the diagnostic criteria for definite familial hypercholesterolemia outlined by the Simon Broome Register Group (Appendix C) or WHO/Dutch Lipid Network (score >8; Appendix D);
5. Must have a fasting LDL-C ≥2.6 mmol/L (100 mg/dL); and
6. Must be on a stable or maximally tolerated dose (≥4 weeks prior to screening) of an approved statin (rosuvastatin ≤20 mg daily, atorvastatin ≤80 mg daily), with or without ezetimibe.

Exclusion Criteria

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

1. Homozygous familial hypercholesterolemia;
2. Low-density lipoprotein (LDL) or plasma apheresis within 2 months prior to randomization;
3. New York Heart Association class III or IV heart failure, or known left ventricular ejection fraction <30%;

4. Uncontrolled cardiac arrhythmia, including confirmed QT interval corrected using Fridericia's formula (QTcF) >450 msec for males and >470 msec for females at the screening electrocardiogram (ECG) assessment;
5. Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke within 3 months prior to randomization;
6. Type 1 diabetes, or newly diagnosed or uncontrolled type 2 diabetes (hemoglobin A1c [HbA1c] >8%);
7. History of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening;

   Note: Significant alcohol consumption is defined as average of >20 g/day in female patients and >30 g/day in male patients;
8. Hyperthyroidism;
9. Thyroid replacement therapy
10. Hypothyroidism;

    Note: If TSH is up to 1.5 x ULN on screening with normal free T4, one repeat test is allowed to confirm the elevation in TSH. If TSH and free T4 are normal upon repeat testing, patient may be included. Patients with a history of thyroid hormone replacement therapy or patients who have discontinued thyroid hormone replacement therapy (including thyroxine) ≥2 months prior to randomization may be included in the study if this criterion is met;
11. Evidence of chronic liver disease;
12. Hepatitis B, as defined by the presence of hepatitis B surface antigen;
13. Hepatitis C, as defined by the presence of hepatitis C virus (HCV) antibody (anti-HCV) and HCV ribonucleic acid (RNA). Patients with positive anti-HCV who test negative for HCV RNA at screening will be allowed to participate in the study;
14. Serum alanine aminotransferase (ALT) >1.5 × ULN (one repeat allowed);
15. Estimated glomerular filtration rate <60 mL/min;
16. Creatine kinase >3 × ULN (one repeat allowed);
17. History of biliary diversion;
18. Positive for human immunodeficiency virus infection;
19. History of malignant hypertension;
20. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at screening or randomization and confirmed at an unscheduled visit;
21. Triglycerides >5.7 mmol/L (500 mg/dL) at screening and confirmed by repeat assessment;

22. Active, serious medical disease with likely life expectancy <2 years;
23. Active substance abuse, including inhaled or injection drugs within the year prior to screening;
24. Use of any excluded medications or procedures listed in Section 5.6.1;
25. Participation in an investigational new drug trial within the 30 days prior to randomization; or
26. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, or compromise the well-being of the patient.

STUDY DESIGN AND DURATION:

This is a multi-center, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of MGL-3196 in patients with HeFH. Patients who qualify for study inclusion will be randomized to receive one of two 12-week treatments: a once daily oral dosing regimen of MGL-3196, or placebo (randomized 2:1) given orally once daily. Patients will self-administer MGL-3196 once daily each morning, and their statin medication each evening, during the 12-week treatment period.

Screening Period

To participate in the study, patients must be diagnosed with HeFH using standard accepted procedures and meet the study criteria. Patients must first provide written, informed consent and then undergo screening procedures within 14 days prior to randomization. Patients will begin taking their statin and other lipid lowering therapy at night at least 2 weeks before randomization, and will continue this practice for the duration of the study.

Treatment Period

On the morning of Day 1, patients will be randomized in 2:1 fashion to receive either MGL-3196 100 mg or matching placebo. Following randomization, patients will undergo a 12-week treatment period and will periodically return to the study site (visits are planned at Weeks 2, 4, 8, 12 and 16) for assessment of drug exposure, safety laboratories, AEs, vital signs (oral temperature, pulse rate, respiratory rate, and seated blood pressure).

At the week 2 visit, in addition to other labs described below, a PK assessment will be made, that will include a pre-dose fasting MGL-3196 determination. Based on their randomization, patients will then be administered one dose of study drug (100 mg MGL-3196 or placebo) and a 4 hour postdose MGL-3196 PK assessment will be made, while patients are fasting. A 12-lead ECG will be measured at 4 hours postdose after the 4 h blood draw. Patients randomized to MGL-3196 100 mg will receive MGL-3196 60 mg between the week 2 and 4 visits, while patients receiving placebo will continue to receive placebo. At the week 4 visit, patients receiving MGL-3196 will either continue to receive 60 mg or be placed back on 100 mg depending on their week 2 MGL-3196 level 4 h postdose. (Patients with week 2 postdose MGL-3196 blood levels < 1,500 ng/mL will be placed on MGL-3196 100 mg, while patients with MGL-3196 blood levels ≥ 1,500 ng/mL will continue to receive 60 mg.

Chemistry (including calcium and phosphorus) and hematology will be assessed at all study visits; a 12-lead electrocardiogram (ECG) will be performed at all study visits; and coagulation and urinalysis will be performed at baseline and end of study. At all study site

visits, blood samples will be collected for the assessment of thyroid hormone parameters including thyroid stimulating hormone (TSH), total triiodothyronine (T3) and thyroxine (T4), and free T3 (FT3) and free T4 (FT4). Lipids (as described in the secondary objectives) will be assessed at all study visits except for low density lipoprotein (LDL) particle analyses, which will be assessed at baseline, Week 12, and Week 16; LDL-C will be determined by ultracentrifugation at baseline and Week 12. Other biomarker assessments will include [redacted] and [redacted], assessed at all study visits. Follicle-stimulating hormone (FSH), total and free testosterone, luteinizing hormone (LH), creatine kinase MB isoenzyme (CKMB), troponin I, reverse T3, fibrinogen, alkaline phosphatase (ALP) isoenzymes, procollagen type 1 N-terminal propeptide (P1NP), and C-terminal telopeptide (CTX) will be assessed at baseline, Week 12, and Week 16; free testosterone will be calculated from total testosterone, [redacted], and serum albumin. Patients will be evaluated for adverse events throughout the study.

Following the first dose of MGL-3196 and thereafter, the dose of MGL-3196 will be down-titrated if TSH is below the lower limit of normal (LLN) with a >50% change from baseline confirmed on 2 consecutive assessments. Down-titrations will be as follows: the 100 mg dose would be decreased to 80 mg, and an 80 mg dose would be decreased to 60 mg. Following down-titration, TSH testing will resume according to the schedule of procedures. A second down-titration is permitted (i.e. to 40 mg).

A Data Safety Monitoring Board (DSMB) will oversee the study to ensure patient safety and to advise if any dosing alterations are recommended. The DSMB will review safety including thyroid hormone effects, liver-related events (ie, clinically meaningful elevations in liver enzymes alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin), and other efficacy (lipid parameters) and safety data as needed. The DSMB will perform regularly scheduled reviews as well as an additional review if necessary.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

MGL-3196 and matching placebo are available as hard gelatin capsules for oral administration in 40 mg and 60 mg strengths. Patients will be randomized to 1 of 2 treatments: MGL-3196 100 mg or placebo given orally once daily in the morning for 12 weeks. Each patient will receive 2 bottles labeled as A and B. The patient will take 1 capsule from bottle A and 1 capsule from bottle B at each dosing. Each bottle will contain 32 capsules (64 capsules total), enough for 4 weeks + 4 days. After the week 2 visit, all patients receiving MGL-3196 100 mg will receive MGL-3196 60 mg between the week 2 and 4 visits. Based on week 2 PK assessment, at the week 4 visit some patients will be placed back on MGL-3196 100 mg. The patient, study personnel, and Sponsor will remain blinded throughout the study.

EFFICACY VARIABLES:

The primary efficacy parameter is mean percent change from baseline in LDL-C.

The secondary efficacy parameters include the following:

- Mean percent change from baseline in non-HDL-C, ApoB, TC/HDL-C ratio, triglycerides, lipoprotein(a), ApoA1/ApoB ratio, and lipoprotein particle assessment; and
- Absolute percent change from baseline in LDL-C.

- Mean percent change from baseline in LDL-C for all patients on study drug (60-100 mg).
- Mean per cent change from baseline in LDL-C according to MGL-3196 exposure.

SAFETY VARIABLES:

Safety variables to be assessed include safety laboratory tests, vital signs, 12-lead ECG with rhythm strip, physical examinations, assessment of adverse events, and clinic assessments.

PHARMACOKINETICS:

Blood samples for PK assessments will be obtained pre-dose from patients at the Baseline Visit (Day 1), Weeks 2, 8, and 12, and the Early Termination Visit. Patients will be instructed not to take study drug prior to PK sampling at these visits. Blood samples for PK assessments will be obtained 4 hours post-dose from patients at Week 2.

STATISTICAL ANALYSES:

Study Populations:

The Intent-to-Treat (ITT) Population will include all patients who are randomized in the study and receive at least 1 dose of study medication. The ITT Population will be used for all efficacy analyses. The Per Protocol Population will include all ITT patients who finish the Week 12 visit with valid LDL-C measurements and do not have any major protocol deviations. Patients who are <80% compliant over the course of the 12-week Treatment Period will not be included in the Per Protocol Population. The Safety Population will include all patients who are randomized in the study and receive at least 1 dose of study medication and will be used for all safety analyses.

Demographics, disposition, and study populations will be summarized descriptively.

Efficacy:

The primary efficacy variable will be the change in LDL-C from baseline to Week 12. Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) at all visits and change from baseline will be provided. The primary efficacy analysis will be analyzed with an analysis of covariance (ANCOVA) model with treatment as a factor and baseline LDL-C as a covariate. Determinations for the 100 (and 60) mg groups will be based on all 12 weeks of the study, including the first two weeks (Week 0-2) in which all patients were on 100 mg and the second two weeks (Week 2-4) when all patients down-titrated to 60 mg. The assigned group (60 or 100 mg) will be based on the dose at Week 4 to Week 12. For any patients in the ITT Population with a missing primary efficacy parameter, the last observation carried forward method will be used. The multiplicity (MGL-3196 100 mg versus placebo and MGL-3196 60 mg versus placebo) will be controlled by Dunnett's Test. The primary efficacy analysis will be performed based on the ITT Population and repeated based on the Per Protocol Population.

For the continuous secondary efficacy variables, the same ANCOVA model will be used. Normality will be tested for the model residuals. For certain efficacy variables, logarithm transformation may be performed prior to fitting the ANCOVA model. For the categorical

secondary efficacy variables, Fisher's exact test will be used to compare the odds ratio between MGL-3196 doses versus placebo.

The same efficacy analyses used for the secondary efficacy variables will be used for any potential exploratory efficacy variables.

Subgroup analysis of the primary efficacy variable and/or selected secondary/other efficacy variables may be performed, such as gender (male/female), body mass index (≥30 kg/m^2 or <30 kg/m^2), age group (≥median or <median), and baseline thyroid status.

Safety:

The safety endpoints for this study include: safety laboratory tests, vital signs, 12-lead ECGs, physical examinations, assessment of adverse events, and clinic assessments.

The adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities. Treatment-emergent adverse events (TEAEs) will be defined as adverse events that are new or worsening after the first dose of study drug. A general summary of patients with TEAEs and serious adverse events (SAEs) will be tabulated with numbers and percentages of patients, and repeated for severity and relationship to study drug per treatment group. The number of adverse events leading to withdrawal and SAEs leading to death will also be summarized. The incidence of TEAEs will be summarized by body system and treatment group.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from the baseline. The values that are <LLN or >ULN of the reference range will be flagged. Those values or changes in values that are identified as being clinically significant will be flagged. Laboratory abnormalities of special interest will be summarized.

SAMPLE SIZE DETERMINATION:

Up to 105 patients in total will be randomized to 1 of 2 treatments (70 patient to MGL-3196, 35 patients to placebo). It is estimated that the treatment difference of percent change in LDL-C from baseline to Week 12 between any dose of the MGL-3196 group and the placebo group is about -20%. With a common standard deviation for the change in LDL-C at 20%, 27 patients per group to complete the Week 12 visit will provide 90% power with a two-sample t-test. The significance level is set as 0.025 for the consideration of multiplicity in comparisons of 2 daily dosing regimens of MGL 3196 vs. placebo group. The enrollment size is designed to allow for dropouts before the 12 week visit, and as such, patients who drop out of the study will not be replaced.

SITES: Approximately 13 sites in Europe.

SPONSOR:

Madrigal Pharmaceuticals, Inc.
Four Tower Bridge, 200 Barr Harbor Drive, Suite 400
West Conshohocken, PA 19428
USA
Telephone: 610-220-7260

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANGPTL3	Angiopoietin-like 3
anti-HCV	Hepatitis C antibody
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ApoCIII	Apolipoprotein CIII
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CKMB	Creatine kinase MB isoenzyme
CRA	Clinical research associate
CTA	Clinical trial authorization
CTX	C-terminal telopeptide
CV	Cardiovascular
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FT3	Free triiodothyronine
FT4	Free thyroxine
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCVAb	Hepatitis C virus antibody
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
hsCRP	High-sensitivity C-reactive protein
ICF	Informed consent form

Abbreviation	Definition
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	Intrauterine device
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NASH	Non-alcoholic steatohepatitis
Non-HDL-C	Non-high-density lipoprotein cholesterol
OATP	Organic anion-transporting polypeptide
P1NP	Procollagen type 1 N-terminal propeptide
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
PT	Prothrombin time
QTcF	QT interval corrected using Fridericia's formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SHBG	Sex hormone-binding globulin
T3	Triiodothyronine
T4	Thyroxine
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
THR	Thyroid hormone receptor
THR-α	Thyroid hormone receptor alpha
THR-β	Thyroid hormone receptor beta
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background

Madrigal Pharmaceuticals is developing MGL-3196 for the treatment of HeFH in adults receiving maximally tolerated statin therapy who require additional lowering of low density lipoprotein cholesterol (LDL-C). Despite advances in treatment, approximately 70% of high-risk cardiovascular (CV) patients do not achieve low-density lipoprotein cholesterol (LDL-C) goals, and as many as 10% of hypercholesterolemic patients do not tolerate statins.[1,2] Elevated LDL-C levels are associated with CV disease, including myocardial infarctions and strokes, and drugs such as statins that lower LDL-C also reduce CV morbidity and mortality.

Heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH) are genetic disorders characterized by severe debilitating dyslipidemia and early onset CV disease. Individuals with HeFH typically have LDL-C levels approximately double that of unaffected siblings. HeFH is most commonly caused by mutations of the LDLR gene. If untreated, early onset coronary artery disease will likely develop in HeFH patients. The prevalence of HeFH is estimated to be 1 in 500 and may be as high as 1 in 200. Despite treatment with newer therapies (ie, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) and standard care (which includes statins and ezetimibe), some HeFH patients are not achieving their LDL-C goal.[3] A recent large registry study of HeFH patients revealed that patients receiving maximal therapy (i.e., statins with a potency of >45% LDL-C reduction plus at least another lipid-lowering agent) only 11.2% reach target LDL-C levels of <100 mg/dL.[4]

Thyroxine (T4) via its active derivative, T3, provides beneficial metabolic effects on cholesterol, triglycerides, and liver triglyceride levels, primarily through action at the THR-β, the predominant hepatocyte THR.[5,6,7,8,9] However, excessive levels of thyroid hormone can lead to adverse effects, particularly in the heart and bones that are primarily mediated by the THR-α receptor which is the major systemic thyroid hormone receptor.[10,11] MGL-3196 is a selective THR-β agonist with actions in the liver that is designed to avoid those systemic actions mediated through THR-α and the central thyroid action suppression observed with previous analogues.

There are several rationales for the use of MGL-3196 for the treatment of patients with genetic dyslipidemias, including HeFH and HoFH. Specifically, thyroid receptor ß agonists have the potential to reduce LDL cholesterol by both LDL-receptor dependent and independent mechanisms, which include reduction in circulating PCSK9,[12] stimulation of hepatic cholesterol metabolism and excretion, potential reduction of ANGPTL3, and direct reduction of ApoB. The effect of thyroid ß receptor agonism to reduce cholesterol in familial hypercholesterolemia (FH) has been demonstrated in mouse LDL-receptor knockout mice[13] and in humans with HeFH treated with an earlier thyroid agonist, eprotirome.[14] Thyroid beta agonists are one of the few mechanisms that has the potential to reduce lipoprotein(a), an atherogenic lipoprotein particle that is frequently elevated in patients with FH. MGL-3196 potently reduces triglycerides, providing additional cardiovascular benefit. In addition, MGL-3196's mechanism is complementary to statins and ezetimibe because thyroid ß receptor agonists do not affect cholesterol synthesis pathways or intestinal absorption of cholesterol.

Thyroid hormone receptor analogs demonstrating an improved therapeutic window between beneficial lipid effects and adverse systemic effects have been developed and tested in clinical trials and demonstrated validation of cholesterol and triglyceride lowering.[15,16] However, eprotirome and other analogs also demonstrated safety issues that resulted in discontinuation of clinical development. These include low margins relative to doses that suppress the central thyroid axis, elevated liver enzymes in Phase 1,2 and 3 studies, and other safety issues such as formation of a nitrated mutagenic impurity at gastric pH and collagen damage in a preclinical toxicology study.[17,18] MGL-3196 has shown absence of these safety issues in preclinical and in clinical studies, so far, as described below.

1.1.1 Profile of MGL-3196, Preclinical and Clinical Data

MGL-3196 is a liver-directed, orally active, partial agonist for the thyroid hormone receptor (THR), with approximately 28-fold selectivity for the beta receptor compared to the active thyroid hormone, triiodothyronine (T3). MGL-3196 was selected for clinical development based on its enhanced THR-ß selectivity in functional THR assays and its greatly improved safety in preclinical animal models relative to other THR analogues and T3.[19] Unlike previous clinical analogues which are, in fact, potent at the alpha receptor like thyroid hormone, MGL-3196 is highly THR-ß selective in a functional coactivator recruitment assay and has virtually no THR-α activity.[19] Liver uptake is mediated by hepatic transporters and, systemic exposure is limited by high protein binding and low tissue penetration outside the liver. In preclinical animal studies, MGL-3196 showed rapid and robust lowering of non-HDL cholesterol, triglycerides, and liver triglycerides, differentiating MGL-3196 from statins and other lipid-lowering agents. In a rabbit model, MGL-3196 showed excellent lipid lowering, including cholesterol and triglycerides when administered alone, and an additive effect of MGL-3196 was observed when administered in combination with atorvastatin.

Preclinical studies, including acute, subchonic, reproductive and chronic animal toxicology studies support the Phase 2 studies. The toxicities observed in both toxicological animal species, rats and dogs, were generally reversible, reflective of pharmacology on the drug target, and were not serious or life-threatening. Between the range of possible clinical doses (80-120 mg per day) a dose of 80 mg is 11,13 fold, and 120 mg is 5,6 fold below the NOAEL in the rat and dog, respectively (Investigator Brochure) and 29-49 fold below the maximum dose that was generally well tolerated, and, while not the NOAEL, in rat was due to monitorable HPT suppression, and in dog, generally monitorable biliary hyperplasia which was associated with elevated ALP. In rats or dogs, no histologic effects on cartilage (or bone) were observed at any dose (NOEL in dogs 62 fold relative to expected clinical exposure at 80 mg), clearly differentiating MGL-3196 from eprotirome.

To date, a total of 129 healthy volunteers have received oral doses of MGL-3196 ranging from single doses of 0.25 to 200 mg, to multiple once-daily oral doses from 5 to 200 mg for up to14 days. The single and multiple ascending dose studies were placebo controlled.

- A two-week multiple dose study (VIA-3196-02, NCT01519531) was conducted at doses of 5, 20, 50, 80, 100, and 200 mg per day in healthy subjects with mildly elevated low density lipoprotein (LDL) cholesterol (> 110 mg/dL).

- MGL-3196 was well tolerated at all doses with no dose-related adverse events or liver enzyme, ECG or vital-sign changes, except for a trend in diastolic BP reduction at the highest doses. There were no changes in standard laboratory safety tests including liver enzymes.
- Doses ranging from 50−200 mg demonstrated highly statistically significant reductions relative to placebo of up to: 30% for LDL cholesterol (range, p = .05-<.0001); 28% for non- high density lipoprotein (HDL) cholesterol (range, p = .027-.0001); 24% for Apolipoprotein B (range, p = .008-.0004), and statistical trends of up to 60% reduction in triglycerides (TG) (range, p = .13-.016). The near maximal lipid effects were observed at a dose of 80 mg daily.
- Lipid lowering effects were confirmed in two Phase 1 clinical drug interaction studies in which either 100 or 200 mg of MGL-3196 was dosed in healthy volunteers for 9-11 days and on one or more day received a single dose of 20 mg simvastatin, 10 mg rosuvastatin or 20 mg atorvastatin. In these studies, the lipid lowering effects were even more pronounced than in the MAD, including a very significant reduction of 45% in TGs in subjects with elevated TGs, Lp(a) lowering of up to 40% in patients with measurable Lp(a), and up to 42% LDL-C lowering, the LDL-C result suggesting the potential for complementarity with statins.
- Overall, in the Phase 1 studies, there were no TEAEs including dose-related AEs consistently associated with MGL-3196 dosing and no laboratory abnormalities including liver enzyme abnormalities.
- In the multiple ascending dose study, subjects receiving the highest dose (200mg) experienced small reversible reductions in prohormone T4 levels, without an effect on active hormone T3, or TSH, that is considered most likely due to increased hepatic T4 deiodination and conversion to the active hormone T3. Importantly, no evidence of central thyroid axis suppression was observed in the MAD. The Phase 1 safety profile for MGL-3196 clearly differentiates it from previous thyroid analogues tested in Phase 1 studies,[15] and confirms its selective pharmacologic action at the liver THR-β receptor.

1.1.2 Comparative Liver Enzyme Effects

In the MGL-3196 SAD and MAD studies, the clinical laboratory values were considered unremarkable and none of the values outside of the reference range with the exception of lipid markers and T4 levels that were considered attributable to the pharmacology. There were no mean changes of note in hematology, chemistry, including liver and renal function, or in urinalysis. There were no effects on vital signs.

Because other thyroid agonists (eprotirome, Metabasis, MB-7811/ Viking, VK-2809) have reported liver enzyme abnormalities in Phase 1, 2, and 3 studies, a comparative analysis was made of MGL-3196 to other analogues, particularly to results from a recent report of eprotirome's Phase 3 study in HeFH patients.[14,18,20,21] In Phase 1 studies, MB-7811 (now VK-2809) reported ALT and AST elevations peaking at about 1.5x ULN on day 14 of the study[22] KB-2115 (eprotirome) in 14 day Phase 1 described: "the most frequent drug-related adverse events observed were mild increases in transaminase [alanine aminotransferase (ALT) and

aspartate aminotransferase] levels, and one subject, who had elevated ALT before dosing with KB2115 developed a transient increase in ALT of 3-fold the upper level for normal."[20] In a Phase 3 study of eprotirome in HeFH patients, statistically significant increases in AST, ALT, bilirubin and GGT were observed that were evident at week 2 and increased at week 6. The ALT elevations were on average 144-183% and AST 60-114 % increased over baseline. A comparative table showing the two week change in ALT and AST for MGL-3196 from the MAD study and eprotirome in the Phase 3 study is shown (Table 1). Approximately 50% of HeFH patients demonstrate > 1XULN elevation of ALT/AST after two weeks of dosing with eprotirome, whilst none of the subjects treated with clinically relevant doses of MGL-3196 showed AST or ALT elevations in 2 weeks. The results of the comparison must be viewed cautiously because the subjects treated with MGL-3196 as compared with eprotirome are different, HeFH patients typically taking several concomitant medications. In recent data submitted for publication (personal communication, J. Kastelein) the effect of thyroid hormone on liver enzymes (ALT, AST, bilirubin) in normal volunteers given at roughly 5X the replacement thyroxine dose was investigated. The study demonstrated no evidence of ALT/AST elevations in any subjects treated with high clinical doses of thyroxine for 2 weeks. The authors suggest that liver enzyme effects of eprotirome may be off-target, compound-specific or secondary to drug interactions rather than due to thyroid hormone receptor agonism.

Table 1 ALT, AST After Two Weeks of Clinical Dosing; MGL-3196, eprotirome

		Level	ALT		AST	
			Baseline	2 weeks	Baseline	2 weeks
Placebo		NL	12 (100*)	12 (100)	12 (100)	12 (100)
		>ULN	0 (0)	0 (0)	0 (0)	0 (0)
MGL-3196	**5mg**	NL	6 (100)	6 (100)	6 (100)	6 (100)
		>ULN	0 (0)	0 (0)	0 (0)	0 (0)
	20mg	NL	6 (100)	5 (83)	6 (100)	6 (100)
		>ULN	0 (0)	1 (17)	0 (0)	0 (0)
	50mg	NL	4 (66.6)	5 (83)	5 (83)	6 (100)
		>ULN	2 (33.3)	1 (17)	1 (17)	0 (0)
	80mg	NL	5 (83)	6 (100)	5 (83)	6 (100)
		>ULN	1 (17)	0 (0)	1 (17)	0 (0)
	100mg	NL	6 (100)	6 (100)	6 (100)	6 (100)
		>ULN	0 (0)	0 (0)	0 (0)	0 (0)
	200mg	NL	6 (100)	6 (100)	6 (100)	6 (100)
		>ULN	0 (0)	0 (0)	0 (0)	0 (0)

* percentage

Table 1 ALT, AST After Two Weeks of Clinical Dosing; MGL-3196, eprotirome **(Continued)**

		Level	ALT			AST		
			Baseline	2 weeks	6 weeks	Baseline	2 weeks	6 weeks
Placebo		NL	20 (87*)	23 (100)	21 (91)	20 (87*)	23 (100)	19 (83)
		ULN-2ULN	3 (13)		2 (9)	3 (13)		4(17)
Eprotirome	50 µg	NL	18 (75)	7 (29)	5 (21)	21 (88)	8 (33)	8 (33)
		ULN-2ULN	6 (25)	10 (42)	14 (58)	3 (13)	12 (50)	13 (54)
		2ULN-3ULN		5 (21)	3 (13)		4 (17)	3 (13)
		3ULN-4ULN		2 (8)	2 (8)			
	100 µg	NL	20 (91)	9 (41)	4 (18)	20 (91)	11 (50)	5 (23)
		ULN-2ULN	2 (9)	7 (32)	11 (50)	2 (9)	8 (36)	12 (55)
		2ULN-3ULN		4 (18)	3 (14)		3 (14)	3 (14)
		3ULN-4ULN		2 (9)	3 (14)			2(9)
		4ULN-5ULN			1 (5)			

*percentage

1.2 Rationale for Phase 2 HeFH Study Design

Doses of 80-200 mg per day of MGL-3196 appeared to have similar effects on lipids after 14 days of dosing in a modest number of otherwise-healthy volunteers with mildly elevated LDL-C; effects in patients with HeFH or in individuals dosed for longer periods may differ. Results of the completed clinical studies, including robust lipid changes observed in the MAD and MGL-3196-03, suggest that MGL-3196 is suitable for once-daily dosing, and that it can be dosed with or without food. Based on the dose-related lipid effects, the doses of MGL-3196 planned for the Phase 2 study in HeFH patients is 100 mg/day (range of projected mean exposure ~4000−9000 ng*hr/ml), to be given once-daily without regard to food.

Patients with HeFH typically take high dose statins, particularly atorvastatin and rosuvastatin with ezetimibe[21,23] to achieve therapeutic targets. MGL-3196's mechanism of cholesterol lowering is complementary to statins.[5] MGL-3196 provides additional benefits, potently lowering triglycerides and, like other thyroid agonists appears to reduce Lp(a), a particularly atherogenic particle frequently elevated in HeFH, including severe HeFH.

1.2.1 Drug Interaction Studies with Statins

A Phase 1 clinical drug interaction study (MGL-3196-03) was conducted between MGL-3196 200 mg per day (steady-state) and rosuvastatin (10 mg) that indicated that there was an increase in rosuvastatin exposure (1.8x) felt to be mediated by the effect of high gut levels of MGL-3196 dosed at 200 mg to inhibit the intestinal transporter BCRP (IC_{50}=22 uM), thereby increasing the absorption of rosuvastatin. This interaction is predicted to be less at a dose of 100 mg per day (~1.6x). Notably, a gut interaction will not diminish the lipid lowering effects of rosuvastatin. Rather as observed in Asians who frequently have BCRP polymorphisms that increase the

exposure to rosuvastatin, a lower rosuvastatin dose will be effective.[24] Therefore as discussed below, the maximal dose of rosuvastatin used in this Phase 2 study will be 20 mg, a two-fold reduction relative to the maximal rosuvastatin dose of 40 mg. To further mitigate an interaction, doses will be staggered with MGL-3196 (dosed in AM) and up to 20 mg rosuvatatin (dosed at night).

A drug interaction study was conducted (MGL-3196-04) between MGL-3196 100 mg per day (at steady-state) and atorvastatin (20 mg) that indicated that there was a mild increase in atorvastatin exposure (1.35x) also felt to be mediated by interactions in the intestine (mild BCRP (IC_{50}=22uM) and weak CYP3A4 inhibition (IC_{50}=200uM)). This mild gut interaction will be mitigated by staggered dosing of MGL-3196 (dosed in AM) with up to 80-mg atorvastatin dosed at night.

In summary, once-daily doses of 100mg (or 60mg after dose adjustment) MGL-3196 and the proposed statin dosing regimens in this 12 week randomized blinded placebo controlled clinical trial are as follows:

- Statins will be dosed at night, MGL-3196 in the morning
- Rosuvastatin, up to 20 mg will be allowed
- Atorvastatin, up to 80 mg will be allowed
- Simvastatin, fluvastatin and other statins will be excluded

Ezetimibe will be allowed in MGL-3196-06. Ezetimibe is commonly used in HeFH patients, given at low dose and has few drug interactions.[25] Given data suggesting that MGL-3196 may increase cholesterol excretion from the liver (increased ABCG5/8 liver gene expression, preclinical data),[26] an agent, ezetimibe, that decreases intestinal absorption of cholesterol may be mechanistically complementary to MGL-3196.

1.2.2 Dose Selection for Phase 2

MGL-3196-06 employs a simple adaptive design, that will optimize dose for individuals randomized to MGL-3196. Based on studies in 129 individuals safely dosed for up to two weeks with MGL-3196, at doses ranging from 50- 200 mg per day, MGL-3196 drug exposure shows variability in exposure between individuals and higher exposure in some individuals, particularly at the 200 mg dose, which will not be used in the Phase 2 HeFH study. This is similar to statins, which are also liver-directed drugs that interact with liver and gut uptake transporters. MGL-3196 exposures are less variable at the lower doses, including 60-100 mg, that will be studied in this Phase 2 study. There are no studies that suggest that exposure to MGL-3196 will be different in patients with HeFH or that HeFH patients have consistent alterations in drug metabolizing enzymes or transporters which may be involved in MGL-3196 uptake by the gut or liver. Unlike statins, there has been no myopathy associated with higher drug exposures of MGL-3196 in humans or animal studies; nonetheless, the design of the HeFH Phase 2 trial is adaptive in that

dose adjustments of MGL-3196 will be made after 2 weeks of dosing to optimize exposure for the individual patient.

MGL-3106 exposure variability, which may relate to polymorphisms in drug metabolizing enzymes and transporters, may occur in some (~25-30%) patients in the HeFH study who may have higher than the target exposure (4000-9000 ng*hr/ml) to MGL-3196 at the 100 mg dose. A few patients (10%) (likely to be non-LDL responders) may have drug levels lower than the target exposure. Therefore, the trial design is adaptive to optimize both safety and efficacy. Randomization will be 2:1, 100 mg MGL-3196 to placebo. The drug level of MGL-3196 reaches steady state in a few days. At the Week 2 clinic visit, an assessment of MGL-3196 PK will be performed, including measurement of the pre-dose and T_{max} (4 h) levels of MGL-3196. These two assessments will allow an accurate assessment of MGL-3196's total exposure. Between weeks 2-4, pending results of the PK measurements, all patients randomized to drug will be treated with 60 mg of MGL-3196. Based on the C_{max} value of MGL-3196 at Week 2, an unblinded clinical pharmacologist will assign MGL-3196 dose to the time period, Weeks 4-12. At Week 4, patients who had a Week 2 $C_{max} \geq 1500$ ng/ml will continue on 60 mg of MGL-3196 and those with $C_{max} < 1500$ ng/ml will be placed back on 100 mg/day.

The primary endpoint will be determined as change from baseline LDL-C for all patients on 100 mg MGL-3196 from week 4-12 relative to placebo the "100 mg group" (a similar calculation will be made for those who continue from Week 4-12 on the 60 mg dose, the "60 mg group"); secondary endpoints will include LDL-C lowering in all patients on MGL-3196 relative to placebo (for 12 weeks), and LDL-C lowering according to exposure to MGL-3196. Additional secondary endpoints will include change from baseline in other lipids including ApoB, nonHDL-C, Lp(a), and TGs.

The exposure levels of statins will also be assessed at baseline and Week 2 (two time points) and pre-dose PK samples will be collected throughout the study. Patients will record the exact time they took the statin the evening before the clinic visit. This will allow the unblinded clinical pharmacologist to determine if there is any unexpected effect on statin exposure related to MGL-3196 dosing. Any changes in statin levels will be monitored by the DSMB and medical monitors.

1.2.3 Safety Monitoring

Careful safety monitoring will be performed including assessment of safety labs, vital signs, ECGs, drug levels to help assure patient safety during this Phase 2 study, particularly during the first few weeks when drug levels will be established. As discussed, a DSMB (including lipid, thyroid, liver and statistical experts) will oversee the study to ensure patient safety and to advise if any dosing alterations are recommended. The DSMB will review safety including thyroid hormone effects, liver-related events (ie, clinically meaningful elevations in liver enzymes ALT, AST, and bilirubin), muscle and cardiovascular effects, and other efficacy (lipid parameters) and safety data as needed. The DSMB will perform regularly scheduled reviews.

Biomarkers of thyroid action, [redacted] TSH, free T4 and free T3 levels will be assessed at study visits. TSH levels will be monitored in the Phase 2 studies as described in the protocol, and downward dose adjustments will be made in any patients who show significant reduction of TSH on two occasions of at least 50% and below the normal range. However, such a reduction in TSH is extremely unlikely. The target exposures at the clinical doses to be used in the Phase 2 studies

are in the range of 4-9000 ng*hr/ml, at least 10 fold lower than exposures where modest, reversible TSH suppression might be anticipated (IB). Small decreases in TSH within the normal range might be observed in HeFH patients treated with MGL-3196 because we anticipate that hepatic T3 production may increase with MGL-3196 treatment, and T3 (the active thyroid hormone) is the key regulator of TSH.

Small decreases in prohormone FT4 of 20% but remaining within the reference range such as observed in MGL-3196 Phase 1 studies are not considered to be clinically meaningful. Most recent human data suggest that maintaining a normal level of active hormone FT3 may be sufficient to establish euthyroidism.[27] In the Phase 1 MAD study, a single subject on the 200 mg dose with the highest drug exposure in the study had a FT4 below the standard reference range (0.7 ng/dL), and in MGL-3196-03, a few subjects had levels of 0.7 ng/dL; in MGL-3196-04, a few subjects, 0.9 ng/dL. After two weeks of dosing in the MAD study, most FT4 levels appeared to reach steady state. Per thyroid expert advice, given the short duration of the HeFH study (12 weeks), and normal TSH and FT3, dose adjustments will not be made to maintain FT4 levels above 0.7 ng/dL.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the effect of each of two separate treatment groups (the "100 mg group" and the "60 mg group") of once-daily oral dose of MGL-3196 and matching placebo on the percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in patients with HeFH.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the safety profile, including any changes in thyroid axis hormones, and tolerability of once-daily oral dosing regimen of MGL-3196 versus placebo after 12 weeks in patients with HeFH;
- To determine the effect of once-daily oral dosing regimen of MGL-3196 versus placebo for 12 weeks on the percent change from baseline on the following assessments in patients with HeFH:
  - Non-high-density lipoprotein cholesterol (non-HDL-C),
  - Apolipoprotein B (ApoB),
  - Total cholesterol/high-density lipoprotein cholesterol (HDL-C) ratio,
  - Triglycerides,
  - Lipoprotein(a),
  - Apolipoprotein A1 (ApoA1)/ApoB ratio, and
  - Lipoprotein particle assessment; and
- To determine the effect of once-daily oral MGL-3196 100 mg versus placebo for 12 weeks on the absolute change from baseline in LDL-C in patients with HeFH.
- To determine the effect of all patients (100 and 60 mg groups) on per cent change from baseline in LDL-C
- The determine the effect of exposure to MGL-3196 on LDL-C lowering.

2.3 Exploratory objectives

- [redacted]

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a multi-center, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of MGL-3196 in patients with HeFH. Patients who qualify for study inclusion will be randomized to receive one of two 12-week treatments: once daily oral dosing regimen of MGL-3196, or placebo (randomized 2:1) given orally once daily. Patients will self-administer MGL-3196 once daily each morning, and their statin medication each evening, during the 12-week treatment period.

To participate in the study, patients must be diagnosed with HeFH using standard accepted procedures and meet the study criteria. Patients must first provide written, informed consent and then undergo screening procedures within 14 days prior to randomization. Patients will begin taking their statin and other lipid lowering therapy at night at least 2 weeks before randomization, and will continue this practice for the duration of the study.

On the morning of Day 1, patients will be randomized in 2:1 fashion to receive either MGL-3196 100 mg or matching placebo. Following randomization, patients will undergo a 12-week treatment period and will periodically return to the study site (visits are planned at Weeks 2, 4, 8, 12 and 16) for assessment of drug exposure, safety laboratories, AEs, vital signs (oral temperature, pulse rate, respiratory rate, and seated blood pressure).

At the week 2 visit, in addition to other labs described below, a PK assessment will be made, that will include a pre-dose fasting MGL-3196 determination. Based on their randomization, patients will then be administered one dose of study drug (100 mg MGL-3196 or placebo) and a 4 hour postdose MGL-3196 PK assessment will be made, while patients are fasting. A 12-lead ECG will be measured at 4 hours postdose after the 4 h blood draw. Patients randomized to MGL-3196 100 mg will receive MGL-3196 60 mg between the week 2 and 4 visits, while patients receiving placebo will continue to receive placebo. At the week 4 visit, patients receiving MGL-3196 will either continue to receive 60 mg or be placed back on 100 mg depending on their week 2 MGL-3196 level 4 h postdose. (Patients with week 2 postdose MGL-3196 blood levels < 1,500 ng/mL will be placed on MGL-3196 100 mg, while patients with MGL-3196 blood levels ≥ 1,500 ng/mL will continue to receive 60 mg.

Chemistry (including calcium and phosphorus) and hematology will be assessed at all study visits; a 12-lead electrocardiogram (ECG) will be performed at all study visits; and coagulation and urinalysis will be performed at baseline and end of study. At all study site visits, blood samples will be collected for the assessment of thyroid hormone parameters including thyroid stimulating hormone (TSH), total triiodothyronine T3 and thyroxine T4, and free T3 (FT3) and free T4 (FT4). Lipids (as described in the secondary objectives) will be assessed at all study visits except for low-density lipoprotein (LDL) particle analyses, which will be assessed at baseline, Week 12, and Week 16; LDL-C will be determined by ultracentrifugation at baseline and Week 12. Other biomarker assessments will include [redacted] and high-sensitivity C-reactive protein (hsCRP), assessed at all study visits. Follicle-stimulating hormone (FSH), total and free testosterone, luteinizing hormone (LH), creatine kinase MB isoenzyme (CKMB), troponin I, reverse T3, fibrinogen, alkaline phosphatase (ALP) isoenzymes, procollagen type 1 N-terminal propeptide (P1NP), and C-terminal telopeptide (CTX) will be assessed at baseline, Week 12, and Week 16; free testosterone will be calculated from total

testosterone, [redacted], and serum albumin. Patients will be evaluated for adverse events throughout the study.

Following the first dose of MGL-3196 and thereafter, the dose of MGL-3196 will be down-titrated if TSH is below the lower limit of normal (LLN) with a >50% change from baseline confirmed on 2 consecutive assessments. Down-titrations will be as follows: the 100 mg dose would be decreased to 80 mg, and an 80 mg dose would be decreased to 60 mg. Following down-titration, TSH testing will resume according to the schedule of procedures. A second down-titration is permitted (i.e. to 40 mg).

A Data Safety Monitoring Board (DSMB) will oversee the study to ensure patient safety and to advise if any dosing alterations are recommended. The DSMB will review safety including thyroid hormone effects, liver-related events (ie, clinically meaningful elevations in liver enzymes alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin), and other efficacy (lipid parameters) and safety data as needed. The DSMB will perform regularly scheduled reviews as well as an additional review if necessary.

3.2 Study Indication

The indication for this study is the reduction of LDL-C in patients with HeFH.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

The population for this study is male and female patients ≥18 years of age who have met the diagnostic criteria for HeFH outlined by the Simon Broome Register Group (Appendix C) World Health Organization (WHO)/Dutch Lipid Network (score >8; Appendix D).

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

1. Must be willing to participate in the study and provide written informed consent;
2. Male and female adults ≥18 years of age;
3. Female patients of child bearing potential with negative serum pregnancy (beta human chorionic gonadotropin) test who are not breastfeeding, do not plan to become pregnant during the study, and agree to use effective birth control (ie, condoms, diaphragm, non-hormonal intrauterine device [IUD], or sexual abstinence [only if this is in line with the patient's current lifestyle]) throughout the study and for at least 1 month after study completion; hormonal contraception (estrogens stable ≥3 months) and hormonal IUDs are permitted if used with a secondary birth control measure (eg, condoms); OR female patients of non-child bearing potential (ie, surgically [bilateral oophorectomy, hysterectomy, or tubal ligation] or naturally sterile [>12 consecutive months without menses]); male patients who have sexual intercourse with a female partner of child bearing potential from the first dose of study drug until 1 month after study completion must either be surgically sterile (confirmed by documented azoospermia >90 days after the procedure) OR agree to use a condom with spermicide. All male patients must agree not to donate sperm from the first dose of study drug until 1 month after study completion;
4. Must have a diagnosis of HeFH by genetic testing or by having met the diagnostic criteria for definite familial hypercholesterolemia outlined by the Simon Broome Register Group (Appendix C) or WHO/Dutch Lipid Network (score >8; Appendix D);
5. Must have a fasting LDL-C ≥2.6 mmol/L (100 mg/dL); and
6. Must be on a stable or maximally tolerated dose (≥4 weeks prior to screening) of an approved statin (rosuvastatin ≤20 mg daily, atorvastatin ≤80 mg daily), with or without ezetimibe.

4.2 Exclusion Criteria

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

1. Homozygous familial hypercholesterolemia;
2. Low-density lipoprotein (LDL) or plasma apheresis within 2 months prior to randomization;
3. New York Heart Association class III or IV heart failure, or known left ventricular ejection fraction <30%;
4. Uncontrolled cardiac arrhythmia, including confirmed QT interval corrected using Fridericia's formula (QTcF) >450 msec for males and >470 msec for females at the screening electrocardiogram (ECG) assessment;

5. Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke within 3 months prior to randomization;
6. Type 1 diabetes, or newly diagnosed or uncontrolled type 2 diabetes (hemoglobin A1c [HbA1c] >8%);
7. History of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening;

   Note: Significant alcohol consumption is defined as average of >20 g/day in female patients and >30 g/day in male patients;
8. Hyperthyroidism;
9. Thyroid replacement therapy
10. Hypothyroidism;

    Note: If TSH is up to 1.5 x ULN on screening with normal free T4, one repeat test is allowed to confirm the elevation in TSH. If TSH and free T4 are normal upon repeat testing, patient may be included. Patients with a history of thyroid hormone replacement therapy or patients who have discontinued thyroid hormone replacement therapy (including thyroxine) ≥2 months prior to randomization may be included in the study if this criterion is met;
11. Evidence of chronic liver disease;
12. Hepatitis B, as defined by the presence of hepatitis B surface antigen (HBsAg);
13. Hepatitis C, as defined by the presence of hepatitis C virus (HCV) antibody (anti-HCV) and HCV ribonucleic acid (RNA). Patients with positive anti-HCV who test negative for HCV RNA at screening will be allowed to participate in the study;
14. Serum ALT >1.5 × ULN (one repeat allowed);
15. Estimated glomerular filtration rate <60 mL/min;
16. Creatine kinase >3 × ULN (one repeat allowed);
17. History of biliary diversion;
18. Positive for human immunodeficiency virus (HIV) infection;
19. History of malignant hypertension;
20. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at screening or randomization and confirmed at an unscheduled visit;
21. Triglycerides >5.7 mmol/L (500 mg/dL) at screening and confirmed by repeat assessment;
22. Active, serious medical disease with likely life expectancy <2 years;
23. Active substance abuse, including inhaled or injection drugs within the year prior to screening;
24. Use of any excluded medications or procedures listed in Section 5.6.1;
25. Participation in an investigational new drug trial within the 30 days prior to randomization; or

26. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, or compromise the well-being of the patient.

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 serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent 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 end of treatment visit (Week 12). 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.

5 STUDY TREATMENTS

5.1 Treatment Groups

Patients who qualify for study inclusion will initially be randomized (2:1) to receive once-daily MGL-3196 100 mg or once-daily matching placebo given orally in the morning. All patients randomized to MGL-3196 will initially receive 100 mg QD through the week 2 visit, then 60 mg QD until the week 4 visit. At the week 4 visit, patients receiving MGL-3196 will be placed back on 100 mg if their week 2 MGL-3196 level 4 h postdose is < 1,500 ng/mL and described as the "100 mg group"; if the level of MGL-3196 ≥1500 ng/ml they will continue to receive 60 mg QD for weeks 4-12 and will be described as the "60 mg group". In summary, the assigned treatment groups are as follows:

- Placebo
- "100 mg group": patients administered MGL-3196 100 mg for weeks 1-2, 60mg between week 2-4 visits, and 100 mg for weeks 4-12
- "60 mg group": patients administered MGL-3196 100 mg for weeks 1-2 and 60 mg for weeks 2-12

5.2 Rationale for Dosing

In 2 completed Phase 1 studies, MGL-3196 appeared to be safe and well tolerated at doses up to 200 mg daily for 14 days. No safety concerns were observed during either study. Lipid efficacy data suggested the therapeutic dose to be less than the highest dose of 200 mg as this dose did not show an improved benefit over lower doses and showed more variability in pharmacokinetic (PK) levels.

5.3 Randomization and Blinding

Patients will be randomized 2:1 to study drug or placebo using a computer-generated randomization schedule prepared by [redacted], prior to the start of the study. The number received during randomization will identify the patient throughout the study and will be used in the eCRF.

Patients, the Sponsor, Investigators, and all site personnel involved with dispensing study medication, carrying out study procedures, evaluating patients, entering study data, and/or evaluating study data will be blinded to treatment assignment until database lock. Blinding will be accomplished by providing visually indistinguishable MGL-3196 and placebo capsules. Packaging for MGL-3196 and placebo product will be identical with the exception of a unique bottle identification number on the label.

5.4 Breaking the Blind

Until formal conclusion of the study, patients, Investigators and all site study personnel will remain blinded as to treatment allocation, except in the event of a medical emergency which necessitates unblinding. In the event of a medical emergency when knowledge of the patient's treatment assignment would influence the patient's clinical care, the Investigator should contact the Medical Monitor to describe the emergency.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The MGL-3196 active drug substance, 2-[3,5-Dichloro-4-95-isopropyl-6-oxo-1,6-dihydro-pyridazin-3-yloxy)-phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4]triazine-6-carbonitrile, is a white to tan crystalline powder stable for 60 months at 25°C/60% relative humidity and 6 months at 40°C/75% relative humidity.

MGL-3196 capsules consist of MGL-3196 active ingredient, pregelatinized starch (Starch 1500), colloidal silicon dioxide (Cab-O-Sil), and magnesium stearate encapsulated in #2 Swedish-orange hard gelatin capsules. MGL-3196 capsules are made in accordance with ICH and FDA guidelines.

MGL-3196 capsules are packaged in high-density polyethylene plastic bottles with child-resistant closures. MGL-3196 and matching placebo are available as hard gelatin capsules for oral administration in 40 mg and 60 mg strengths. Product labels will be identical except for a unique identifying code. Patients will receive 2 bottles with the additional labels of A and B. Each bottle will contain 32 capsules (64 capsules total).

5.5.2 Study Drug Preparation and Dispensing

Study drug will be bottled and labeled by [redacted] using current Good Manufacturing Practice. Study drug will be assigned by Interactive Response Technology (IRT) to study site/patients.

5.5.3 Study Drug Administration

Study drug will be administered in the morning at the Week 1, 4, 8, and 12 study visits. Each patient will receive 2 bottles labeled as A and B. The patient will take 1 capsule from bottle A and 1 capsule from bottle B at each dosing. Each bottle will contain 32 capsules (64 capsules total), enough for 4 weeks + 4 days.

5.5.4 Treatment Compliance

Patients will be assessed for study drug compliance at each visit. On Day 1, patients will receive a study drug journal in which to record study drug compliance. Site staff will record the number of capsules taken from each study drug bottle and record this information in the patient's eCRF. If at any visit the patient is <80% compliant, the patient will be counseled on the importance of compliance to the study regimen. If at the end of study, the patient is <80% compliant over the course of the 12-week Treatment Period, the patient will not be included in the Per Protocol Population.

5.5.5 Storage and Accountability

Adequate records on receipt, use, return, loss, or other disposition of medication must be maintained. Other required data includes relevant dates, quantities, unique bottle code, and patient identification for patients who receive study drug. Patients will be instructed to return all unused study medication to the Investigator, in the original bottles. At the end of the study, all unused products will be collected and destroyed according to institutional pharmacy policies and procedures. The study drug will be stored according to manufacturing guidelines (see Section 5.5.1).

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Excluded medications and/or procedures include:

- Major inhibitors of OATP transporters such as gemfibrozil, cyclosporine A, or protease inhibitors;
- Repaglinide or a glitazone such as rosiglitazone (substrates of CYP2C8) or gemfibrozil (inhibitor of CYP2C8);
- Glipizide or tolbutamide treatment;
- Warfarin treatment;
- Fibrates, PCSK9 inhibitors (within 4 months prior to randomization), or niacin;
- Prior or planned (during the study period) upper gastrointestinal surgery, including bariatric surgery (eg, gastroplasty, roux-en-Y gastric bypass);
- GLP-1 analogue or complex oral antidiabetic regimen (3 or more oral antidiabetic drugs). Patients are allowed to be on insulin if there has been no change >10% in unit dose in the 2 months prior to screening, and they are allowed to be on up to 2 oral antidiabetic drugs; and
- Systemic steroids, herbal supplements (eg, kelp), or iodine supplements that can affect thyroid or weight loss medications.

5.6.2 Documentation of Prior and Concomitant Medication Use

All concomitant medications must be recorded in the eCRF. Any prior medication received within 30 days of the first dose of study drug will be recorded in the eCRF. Concomitant treatments that are required to manage a patient's medical condition during the trial will also be recorded in the eCRF.

Patients taking bile acid sequestrants should take them approximately 4-6 hours after taking their MGL-3196 study drug or matching placebo and approximately 4-6 hours prior to their evening statin dose.

6 STUDY PROCEDURES

6.1 Informed Consent

Informed consent will be obtained at the Screening Visit (Day -14 to Day -1) prior to performing any study-related procedures.

6.2 Screening Visit (Day -14 to Day -1)

The following procedures will be performed at the Screening Visit:

- Obtain informed consent;
- Collect demographic information and review medical history;
- Assess eligibility;
- Collect vital signs;
- Measure height and weight (calculate body mass index);
- Perform 12-lead ECG;
- Perform complete physical examination;
- Collect blood samples for the following assessments:
  - Hematology and chemistry;
  - Serum pregnancy test (female patients only);
  - Coagulation panel;
  - Thyroid function test (except TBG);
  - Lipid panel, apolipoproteins, and lipoprotein(a);
  - [redacted]
  - HbA1c;
  - Hepatitis panel, including hepatitis B, HBsAg, HCV, and HCV antibody (HCVAb); and
  - HIV;
- Collect urine sample for the following assessments:
  - Urinalysis, and
  - Urine drug screen;
- Provide diet and lifestyle counseling; and
- Review concomitant medications.
- Verify on stable maximally tolerated dose of atorvastatin or rosuvastatin (up to 20 mg) and adjust statin dosing to once daily in evenings

6.3 Randomization

Patients will be randomized at the Baseline Visit (Day 1).

6.4 Treatment Period – Day 1 Through Day 84

Following randomization to study medication at the Baseline Visit, patients will return for visits and procedures to occur within ±3 days of the scheduled date. In all cases, the patient should arrive at the clinic in the morning after at least 10 hours of fasting, and record the time they took their statin the night before.

6.4.1 Baseline Visit (Day 1)

The following procedures will be performed at the Baseline Visit:

- Assess eligibility;
- Randomize patients;
- Collect vital signs;
- Measure weight;
- Perform 12-lead ECG;
- Perform targeted, symptom-directed physical examination;
- Collect blood samples for the following assessments:
  - Hematology and chemistry;
  - Coagulation panel (prothrombin time [PT] and activated partial thromboplastin time [aPTT] only);
  - Thyroid function test;
  - Lipid panel, apolipoproteins, ApoCIII, and lipoprotein(a);
  - Lipoprotein particle analysis;
  - LDL-C by ultracentrifugation;
  - FSH, total and free (calculated) testosterone, LH, CKMB, troponin I, reverse T3, ALP isoenzymes, P1NP, CTX, and fibrinogen. Free testosterone will be calculated from total testosterone, [redacted], and serum albumin;
  - [redacted];
  - HbA1c;
  - Genomics;
  - Backup sample;
  - [redacted]
  - [redacted]; and
  - Pre-dose PK (measurement of statin level);

- Collect urine sample for the following assessments:
  - Urinalysis, and
  - Human chorionic gonadotropin (if applicable);
- Assign study drug via IRT;
- Dispense study drug for Weeks 1-2; and
- Review concomitant medications and adverse events.

6.4.2 Week 2 (Day 14 [±3 days])

Patient arrives at the clinic in the morning fasting. The following procedures will be performed at Week 2:

- Collect vital signs;
- Measure height and weight (calculate body mass index);
- Perform targeted, symptom-directed physical examination;
- Collect blood samples for the following assessments:
  - Hematology and chemistry;
  - Serum pregnancy test (female patients only);
  - Thyroid function test;
  - Lipid panel, apolipoproteins, ApoCIII, and lipoprotein(a);
  - [redacted]; and
  - Pre-dose and 4-hr post dose PK (for statins and MGL-3196);
- Perform 12-lead ECG at 4 hours post dose (after second blood draw);
- Assess study drug accountability;
- Dispense study drug for weeks 3-4 via IRT;
- Review concomitant medications and adverse events; and
- Verify on statin dose and once daily in evenings.

6.4.3 Week 4 (Day 28 [±3 days])

Patients will arrive at the clinic fasting. The following procedures will be performed at Week 4:

- Collect vital signs;
- Measure height and weight (calculate body mass index);
- Perform targeted, symptom-directed physical examination;
- Collect blood samples for the following assessments:
  - Hematology and chemistry;

- Serum pregnancy test (female patients only);
- Thyroid function test;
- Lipid panel, apolipoproteins, ApoCIII, and lipoprotein(a);
- [redacted] and
- Pre-dose PK;

- Perform 12-lead ECG (after 30 minutes of rest following blood draws);
- Assess study drug accountability;
- Dispense study drug for weeks 5-8 via IRT; and
- Review concomitant medications and adverse events.

6.4.4 Week 8 (Day 56 [±3 days])

The following procedures will be performed at Week 8:

- Collect vital signs;
- Measure height and weight (calculate body mass index);
- Perform 12-lead ECG;
- Perform targeted, symptom-directed physical examination;
- Collect blood samples for the following assessments:
  - Hematology and chemistry;
  - Serum pregnancy test (female patients only);
  - Thyroid function test;
  - Lipid panel, apolipoproteins, ApoCIII, and lipoprotein(a);
  - [redacted];
  - HbA1C; and
  - Pre-dose PK;
- Assess study drug accountability;
- Dispense study drug for weeks 9-12 via IRT; and
- Review concomitant medications and adverse events.

6.4.5 Week 12 (Day 84 [±3 days]) or Early Termination Visit

The following procedures will be performed at Week 12 or at the Early Termination Visit:

- Collect vital signs;
- Measure weight;
- Perform 12-lead ECG;

- Perform targeted, symptom-directed physical examination;
- Collect blood samples for the following assessments:
  - Hematology and chemistry;
  - Serum pregnancy test (female patients only);
  - Coagulation panel;
  - Thyroid function test;
  - Lipid panel, apolipoproteins, ApoCIII, and lipoprotein(a);
  - Lipoprotein particle analysis;
  - LDL-C by ultracentrifugation;
  - [redacted];
  - FSH, total and free (calculated) testosterone, LH, CKMB, troponin I, reverse T3, ALP isoenzymes, P1NP, CTX, and fibrinogen. Free testosterone will be calculated from total testosterone, [redacted], and serum albumin;
  - HbA1c;
  - Backup sample;
  - [redacted]
  - [redacted]; and
  - Pre-dose PK;
- Collect urine sample for urinalysis;
- Assess study drug accountability; and
- Review concomitant medications and adverse events.

6.5 Follow-Up Visit at Week 16 (Day 112 [±3 days])

The following procedures will be performed at the Follow-Up Visit at Week 16:

- Collect vital signs;
- Measure weight;
- Perform 12-lead ECG;
- Perform targeted, symptom-directed physical examination;
- Collect blood samples for the following assessments:
  - Hematology and chemistry;
  - Serum pregnancy test (female patients only);
  - Thyroid function test;
  - Lipid panel, apolipoproteins, ApoCIII, and lipoprotein(a);

- Lipoprotein particle analysis;
- [redacted]; and
- FSH, total and free (calculated) testosterone, LH, CKMB, troponin I, reverse T3, ALP isoenzymes, P1NP, CTX, and fibrinogen. Free testosterone will be calculated from total testosterone, [redacted], and serum albumin; and

- Review concomitant medications and adverse events.

6.6 Early Termination Visit and Withdrawal Procedures

For patients who are withdrawn from the study prior to completion, the procedures described for the Week 12 Visit (Section 6.4.5) will be performed at an Early Termination Visit.

7 EFFICACY ASSESSMENTS

The primary efficacy parameter is mean percent change from baseline in LDL-C.

The secondary efficacy parameters include the following:

- Mean percent change from baseline in non-HDL-C, ApoB, TC/HDL-C ratio, triglycerides, lipoprotein(a), ApoA1/ApoB ratio, and lipoprotein particle assessment; and
- Absolute percent change from baseline in LDL-C.
- Mean percent change from baseline in LDL-C for all patients on study drug (60-100 mg)
- Mean per cent change from baseline in LDL-C according to MGL-3196 exposure

The exploratory efficacy parameters include the following:

- [redacted]
- [redacted]

8 PHARMACOKINETIC ASSESSMENTS

Blood samples for PK assessments will be obtained fasting pre-dose from patients at the Baseline Visit (Day 1), Weeks 2, 4, 8, and 12, and the Early Termination Visit. Blood samples for PK assessment will also be obtained 4 hours post-dose from patients at Week 2 under fasting conditions. Statin PK will also be assessed at baseline and Week 2 visits and may be assessed at later visits.

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 clinical laboratory test variables, will be monitored and documented from the time of informed consent until study participation is complete. Patients should be instructed to report any adverse event that they experience to the Investigator. Beginning at the Screening Visit, Investigators should make an assessment for adverse events at each visit and record the event 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 (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline change in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific 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

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

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.

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/no.

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 (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 (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (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 (concomitant drugs, therapies, complications, etc.) 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, intercurrent diseases-
  - 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 pharmacokinetics of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

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 the 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 hospitalization;
  - Note: Any hospital admission with at least 1 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 (ie, 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 above. 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.

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 [redacted] 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, [redacted] 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 [redacted] or call the [redacted] and fax the completed paper SAE form to [redacted] 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.

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 (eg, patient discharge summary or autopsy reports) to [redacted] 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 or female partner of a male patient becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to [redacted] within 24 hours of being notified. [redacted] 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 Early Termination study procedures will be performed.

The patient or female partner of a male 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 [redacted]. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, 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.

9.6 Informed Consent

All patients will be informed of the nature and purpose of the study. Patients will sign informed consent at the Screening Visit (Day -14 to Day -1), prior to any study procedures being performed.

9.7 Demographic Information

Demographic information including day, month, and year of birth; race; ethnicity; and gender will be collected at the Screening Visit (Day -14 to Day -1).

9.8 Clinical Laboratory Evaluations

All standard blood and urine tests will be performed by a central laboratory. For the purposes of this study, fasting will be defined as nothing by mouth except water for 10 hours. If the patient is not fasting, the Investigator will reschedule the visit as soon as possible but no later than 3 days. Laboratory certification (including expiration date) and normal reference ranges for all laboratories used during the study will be on file with [redacted] prior to study initiation. For a complete list of laboratory assessments that will be performed, see Appendix B. For blood sampling procedures, including information on blood volume, collection tubes, sample processing, storage, and shipping, see the Laboratory Manual for this study.

The Investigator must review and sign all laboratory test reports. The Investigator will be notified if laboratory values are outside of normal range and for alert values. In this case, the Investigator will be required to conduct clinically appropriate follow-up procedures.

The following analytes will be measured at the Screening Visit (Day -14 to Day -1), Baseline Visit (Day 1), and Weeks 2, 4, 8, 12, and 16:

- Standard Chemistry Panel – ALT, albumin, ALP, amylase, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatine kinase, creatinine, direct bilirubin, estimated glomerular filtration rate, gamma-glutamyl transpeptidase (GGT), glucose, inorganic phosphorus, lactate dehydrogenase, lipase, magnesium, potassium, sodium, total bilirubin, total protein, and uric acid; and
- Standard Hematology Panel – hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count and differential.

The following urinalysis analytes will be measured at the Screening Visit (Day -14 to Day -1), Baseline Visit (Day 1), and Week 12: bilirubin, blood, glucose, ketones, leukocyte esterase, microscopy, nitrate, pH, protein, specific gravity, and urobilinogen.

Hepatitis B, HBsAg, HCV, HCVAb, and HIV will be measured at the Screening Visit (Day -14 to Day -1).

A coagulation panel (aPTT, PT, and international normalized ratio [INR]) will be performed at the Screening Visit (Day -14 to Day -1) and Week 12. At the Baseline Visit (Day 1), only aPTT and PT will be performed.

A thyroid function test (TT3, TT4, FT3, FT4, TSH) will be performed at the Screening Visit (Day -14 to Day -1); Baseline Visit (Day 1), and Weeks 2, 4, 8, 12, and 16, TT3, TT4, FT3, FT4, TSH and TBG will be assessed.

A lipid panel, apolipoproteins, and lipoprotein(a) will be measured at the Screening Visit (Day -14 to Day -1). These lipids plus ApoCIII will be measured at Baseline Visit (Day 1), and Weeks 2, 4, 8, 12, and 16. A lipoprotein particle analysis will be performed at the Baseline Visit (Day 1), Week 12, and Week 16, and LDL-C will be determined by ultracentrifugation at the Baseline Visit (Day 1) and Week 12.

Sex hormone binding globulin and [redacted] will be measured at the Screening Visit (Day -14 to Day -1), Baseline Visit (Day 1), and Weeks 2, 4, 8, 12, and 16.

Follicle stimulating hormone, total and free testosterone, LH, CKMB, troponin I, reverse T3, ALP isoenzymes, P1NP, CTX, and fibrinogen will be measured at the Baseline Visit (Day 1), Week 12, and Week 16. Free testosterone will be calculated from total testosterone, [redacted], and serum albumin.

Hemoglobin A1c will be measured at the Screening Visit (Day -14 to Day -1), Baseline Visit (Day 1), and Weeks 8 and 12.

Genomic samples will be collected at the Baseline Visit (Day 1).

Backup blood samples will be collected at Baseline Visit (Day 1) and Week 12 for use if a laboratory evaluation needs to be repeated.

A urine drug screen will be performed at the Screening Visit (Day -14 to Day -1).

Proprotein convertase subtilisin/kexin type 9 and [redacted] will be measured at the Baseline Visit (Day 1) and at Week 12.

9.9 Vital Signs

Vital signs (oral temperature, pulse, respiratory rate, and seated blood pressure) will be measured at the Screening Visit (Day -14 to Day -1), the Baseline Visit (Day 1), and Weeks 2, 4, 8, 12, and 16.

Blood pressure will be measured using a standardized process:

- Patient should sit for 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Use of a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;
- Record the arm used for measurement and use the same arm throughout the study; and
- Measure and record the blood pressure.

Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on the automatic device. A blood pressure reading should be repeated 1 to 2 minutes later, and the second reading should also be recorded to the nearest 2 mmHg mark.

Body weight will be measured at the Screening Visit (Day -14 to Day -1), the Baseline Visit (Day 1), and Weeks 2, 4, 8, 12, and 16. Height will be recorded at the Screening Visit and Weeks 2, 4, and 8. Body weight measurement should be performed with the patient dressed in indoor clothing, shoes removed, and bladder empty. Patients should be weighed on the same scale at all visits. Height measurement should be performed with the patient's shoes removed; the patient's knees should be straightened, head held erect, and eyes forward.

9.10 Electrocardiograms

Twelve-lead ECGs with rhythm strip will be performed at the Screening Visit (Day -14 to Day -1), the Baseline Visit (Day 1), and Weeks 2, 4, 8, 12, and 16. At the Week 2 visit, patients will rest for 30 minutes after the 4 h post-dose blood draw before the ECG is performed.

Twelve-lead ECGs will be performed in triplicate in a consecutive manner after the patient has been resting in the supine position for at least 10 minutes. The ECG will include 12 standard leads and will be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be recorded:

- PR interval,
- QRS interval,
- Heart rate,
- RR interval,
- QT interval,
- QTc interval, and
- QTcF interval.

All ECGs must be evaluated by a qualified reader for the presence of abnormalities.

9.11 Physical Examinations

A complete physical examination will include documentation of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular assessments and will be performed at the Screening Visit (Day -14 to Day -1). Targeted, symptom-directed physical examinations will be performed at all other study visits.

9.12 Diet and Lifestyle Counseling

Patients will be counseled on maintaining a consistent diet, exercise regimen, and lifestyle at the Screening Visit (Day -14 to Day -1).

9.13 Drug Induced Liver Injury Monitoring

With any of the following liver function test elevations, patients should undergo repeat laboratory measurements as soon as possible, preferably within 72 hours (unless otherwise specified), and no later than 1 week. Local laboratory measurements may be used to facilitate follow-up:

- ALT or AST >8 × ULN;
- ALT or AST >3 × ULN and bilirubin >2 × ULN or International Normalized Ratio >1.5 × ULN;
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash, and/or eosinophilia (>5%); and
- ALT or AST >5 × ULN, regardless of symptoms should be followed up within 1 week.

Repeat evaluation should include AST, ALT, prothrombin time/International Normalized Ratio, total bilirubin, alkaline phosphatase, gamma-glutamyltransferase, creatinine, CK, and complete viral hepatitis screen. The patient should be questioned regarding symptoms, as well as potential causative factors. This information, including results and normal ranges of any laboratory parameters collected at a local laboratory, should be collected on the appropriate eCRF. Hepatobiliary ultrasonography and/or consultation with a hepatologist should be considered if clinically indicated.

Abnormal laboratory parameters should be followed at least weekly (more frequently as clinically indicated) until they have returned to baseline or have stabilized.

10 STATISTICS

10.1 Analysis Populations

The Intent-to-Treat (ITT) Population will include all patients who are randomized in the study and receive at least 1 dose of study drug. The ITT Population will be used for all efficacy analyses.

The Per Protocol Population will include all ITT patients who finish the Week 12 Visit with valid LDL-C measurements, have ≥80% treatment compliance, and do not have any major protocol deviations.

The Safety Population will include all patients who are randomized in the study and receive at least 1 dose of study drug and will be used for all safety analyses.

For patients randomized to MGL-3196, the assigned treatment group (60 or 100 mg group) will be based on the dose at Week 4 to Week 12.

10.2 Statistical Methods

10.2.1 Analysis of Efficacy

10.2.1.1 Primary efficacy analysis

The primary efficacy variable will be the change in LDL-C from baseline to Week 12. Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) at all visits and change from baseline will be provided. The primary efficacy analysis will be analyzed with an analysis of covariance (ANCOVA) model with treatment as a factor and baseline LDL-C as a covariate. Determinations for the 100 (and 60) mg groups will be based on all 12 weeks of the study, including the first two weeks (Week 0-2) in which all patients were on 100 mg and the second two weeks (Week 2-4) when all patients down-titrated to 60 mg. The assigned group (60 or 100 mg) will be based on the dose at Week 4 to Week 12. For any patients in the ITT Population with a missing primary efficacy parameter, the last observation carried forward method will be used. The multiplicity (MGL-3196 100 mg versus placebo and MGL-3196 60 mg versus placebo) will be controlled by Dunnett's Test. The primary efficacy analysis will be performed based on the ITT Population and repeated based on the Per Protocol Population.

10.2.1.2 Secondary efficacy analysis

For the continuous secondary efficacy variables, the same ANCOVA model will be used. Normality will be tested for the model residuals. For certain efficacy variables, logarithm transformation may be performed prior to fitting the ANCOVA model. For the categorical secondary efficacy variables, Fisher's exact test will be used to compare the odds ratio between MGL-3196 doses versus placebo.

10.2.1.3 Other efficacy analysis

The same efficacy analyses used for the secondary efficacy variables will be used for any potential exploratory efficacy variables.

10.2.1.4 Subgroup analysis

Subgroup analysis of the primary efficacy variable and/or selected secondary/other efficacy variables may be performed, such as gender (male/female), body mass index (≥30 kg/m^2 or <30 kg/m^2), age group (≥median or <median), and baseline thyroid status.

10.2.2 Analysis of Safety

The safety endpoints for this study include: safety laboratory tests, vital signs, 12-lead ECGs, physical examinations, assessment of adverse events, and clinic assessments.

The adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) will be defined as adverse events that are new or worsening after the first dose of study drug. A general summary of patients with TEAEs and SAEs will be tabulated with numbers and percentages of patients, and repeated for severity and relationship to study drug per treatment group. The number of adverse events leading to withdrawal and SAEs leading to death will also be summarized. The incidence of TEAEs will be summarized by body system and treatment group.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from the baseline. The values that are <LLN or >ULN of the reference range will be flagged. Those values or changes in values that are identified as being clinically significant will be flagged. Laboratory abnormalities of special interest will be summarized.

10.2.3 Data Safety Monitoring Board

A DSMB will oversee the study to ensure patient safety and to advise if any dosing alterations are recommended. The DSMB will review safety including thyroid hormone effects, liver-related events (ie, clinically meaningful elevations in liver enzymes ALT, AST, and bilirubin), and other efficacy (lipid parameters) and safety data as needed. The DSMB will perform regularly scheduled reviews as well as an additional review if necessary.

10.2.4 Sample Size Determination

Up to 105 patients in total will be randomized to 1 of 2 treatments (70 patient to MGL-3196, 35 patients to placebo). It is estimated that the treatment difference of percent change in LDL-C from baseline to Week 12 between any dose of the MGL-3196 group and the placebo group is about -20%. With a common standard deviation for the change in LDL-C at 20%, 27 patients per group to complete the Week 12 visit will provide 90% power with a two-sample t-test. The significance level is set as 0.025 for the consideration of multiplicity in comparisons of 2 daily dosing regimens of MGL-3196 vs. placebo group. The enrollment size is designed to allow for dropouts before the 12-week visit, and as such, patients who drop out of the study will not be replaced.

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 clinical research associate (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 processed using a validated computer system conforming to regulatory requirements.

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 Title 21 of the Code of Federal Regulations (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 adverse events and medical history, and
- WHO 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/Independent Ethics Committee

The IRB/IEC 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/IEC approval has been obtained. The protocol, Investigator's Brochure, Informed Consent Form (ICF), advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and ICH require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. 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 to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

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

For study sites in Europe, it is the responsibility of the Sponsor or their designee (ie, [redacted]) to obtain the approval of the responsible IEC according to the national regulations. The study will only start in these sites once the respective committee's written approval has been given.

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/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient 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 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 enrollment in the study. 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/IEC, 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, European patients 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, Directive 2001/20/EC, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the study 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, and the procedure for reporting 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.

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/IEC, 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, eg, 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 the Sponsor 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

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 patient liability insurance for all patients who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

12.11 Legal Aspects

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

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

13 STUDY ADMINISTRATIVE INFORMATION

13.1 Protocol Amendments

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

13.2 Address List

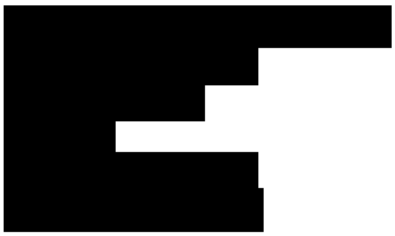
13.2.1 Sponsor

Madrigal Pharmaceuticals, Inc.
Four Tower Bridge, 200 Barr Harbor Drive, Suite 400
West Conshohocken, PA 19428
USA
Telephone: 610-220-7260

13.2.2 Contract Research Organization

13.2.3 Drug Safety

13.2.4 Biological Specimens



13.2.5 Pharmacokinetic Specimens

14 REFERENCES

1. Waters DD, Brotons C, Chiang CW, et al. Lipid Treatment Assessment Project. Lipid treatment assessment project 2: a multinational survey to evaluate the proportion of patients achieving low-density lipoprotein cholesterol goals. Circulation. 2009;120(1):28-34.

2. Joy TR and Hegele RA. Narrative review: statin-related myopathy. Ann Intern Med. 2009;150(12):858-868.

3. 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.

4. Perez de Isla L. at al. Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia: 5-Year SAFEHEART Registry Follow-Up. JACC. 2016 Mar:67(11):1278-85.

5. Baxter JD and Webb P. Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. Nat Rev Drug Discov. 2009 Apr:8(4): 308-320.

6. Grover GJ, Egan DM, Sleph PG, Beehler BC, Chiellini G, Nguyen NH, Baxter JD and Scanlan TS. Effects of the thyroid hormone receptor agonist GC-1 on metabolic rate and cholesterol in rats and primates: selective actions relative to 3,5,3'-triiodo-L-thyronine. Endocrinology. 2004 April;145(4): 1656-1661.

7. Grover GJ, Mellstrom K, Ye L, Malm J, Li YL, Bladh LG, Sleph PG, Smith MA, George R, Vennstrom B, Mookhtiar K, Horvath R, Speelman J, Egan D and Baxter JD. Selective thyroid hormone receptor-beta activation: a strategy for reduction of weight, cholesterol, and lipoprotein (a) with reduced cardiovascular liability. Proc Natl Acad Sci U S A. 2003 Aug 19; 100(17): 10067-10072.

8. Johansson L, Rudling M, Scanlan TS, Lundasen T, Webb P, Baxter J, Angelin B and Parini P. Selective thyroid receptor modulation by GC-1 reduces serum lipids and stimulates steps of reverse cholesterol transport in euthyroid mice. Proc Natl Acad Sci U S A. 2005 July 19;102(29):10297-10302.

9. Morkin E, Pennock GD, Spooner PH, Bahl JJ and Goldman S.Clinical and experimental studies on the use of 3,5-diiodothyropropionic acid, a thyroid hormone analogue, in heart failure. Thyroid. 2002;12(6): 527-533.

10 . Gogakos AI, Duncan Bassett JH and Williams GR. Thyroid and bone. Arch Biochem Biophys. 2010 Nov 1;503(1): 129-136.

11. Klein I and Danzi S. Thyroid disease and the heart. Circulation. 2007 Oct 9;116(15):1725-1735.

12. Bonde Y, Breuer O, Lütjohann D, Sjöberg S, Angelin B, Rudling M. Thyroid hormone reduces PCSK9 and stimulates bile acid synthesis in humans. J Lipid Res. 2014 Nov; 55(11):2408-2415.

13. Goldbert IJ, Huang LS, Huggins LA, et al. Thyroid hormone reduces cholesterol via a non-LDL receptor-mediated pathway. Endocrinology. 2012 Nov;153(11):5143-5149.

14. Sjouke B, Langslet G, Ceska R, et al. Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): a randomized, double-blind, placebo-controlled phase 3 study. Lancet Diabetes Endocrinol. 2014 Jun;2(6):455-463.

15. Erion MD, Cable EE, Ito BR, Jiang H, Fujitaki JM, Finn PD, Zhang BH, Hou J, Boyer SH, van Poelje PD and D. L. Linemeyer DL. Targeting thyroid hormone receptor-beta agonists to the liver reduces cholesterol and triglycerides and improves the therapeutic index. Proc Natl Acad Sci U S A. 2007 Sept 25;104(39): 15490-15495.

16. Dong BJ. How medications affect thyroid function. West J Med. 2000 Feb;172(2): 102-106.

17. Bengsston, P. "Karo Bio terminates the Eprotirome Program" Karo Bio February 14, 2012 http://www.karobio.com/investormedia/pressreleaser/pressrelease?pid=639535.

18. Elbers LP, Kastelein JJ, Sjouke B Thyroid Hormone Mimetics: the Past, Current Status and Future Challenges. Curr Atheroscler Rep. 2016 Mar;18(3):14. doi: 10.1007/s11883-016-0564-7

19. Kelly MJ, Pietranico-Cole S, Larigan JD, Haynes NE, Reynolds CH, Scott N, Vermeulen J, Dvorozniak M, Conde-Knape K, Huang KS, So SS, Thakkar K, Qian Y, Banner B, Mennona F, Danzi S, Klein I, Taub R and Tilley J. Discovery of 2-[3,5-Dichloro-4-(5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yloxy)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro[1,2,4]triazine-6-carbonitrile (MGL-3196), a Highly Selective Thyroid Hormone Receptor beta Agonist in Clinical Trials for the Treatment of Dyslipidemia. J. Med. Chem. 2014;57(10):3912-3923.

20. Berkenstam, A, Kristensen J, Mellstrom K, Carlsson B, Malm J, Rehnmark S, Garg N, Andersson CM, Rudling M, Sjoberg F, Angelin B and Baxter JD. The thyroid hormone mimetic compound KB2115 lowers plasma LDL cholesterol and stimulates bile acid synthesis without cardiac effects in humans. Proc Natl Acad Sci U S A. 105(2): 663-667, 2008.

21. Robinson, JG Management of familial hypercholesterolemia:a review of the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia J Manag Care Pharm. 2013;19(2):139-49.

22. Lian A, Hanley R, Schoenfeld S. Phase 1 Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate Safety, Tolerability and Pharmacokinetics of the Liver-Selective Tr-Beta Agonist Vk2809 (Mb07811) in Hypercholesterolemic Subjects. ACC 2016 J Am Coll Cardiol. 2016; 67(13_S):1932-1932. doi: 10.1016/S0735-1097(16)31933-7.

23. Santos RD et al. Defining severe familial hypercholesterolaemia and theimplications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Lancet Diabetes-Endocrinol 2016 http://dx.doi.org/10.1016/S2213-8587(16)30041-9.

24. Allred AJ, Bowen CJ, Park JW, Peng B, Williams DD, Wire MB, et al. Eltrombopag increases plasma rosuvastatin exposure in healthy volunteers. Br J Clin Pharmacol. 72(2): 321–9, 2011.

25. Simard C, Turgeon J. The pharmacokinetics of ezetimibe. Can J Clin Pharmacol. 2003 Winter;10 Suppl A:13A-20A.

26. Pedrelli M, Pramfalk, C Parini, P. Thyroid hormones and thyroid hormone receptors: Effects of thyromimetics on reverse cholesterol transport World J Gastroenterol 2010 December 21; 16(47): 5958-5964.

27. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the Treatment of Hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid. 2014;24(12):1670-1751.

APPENDIX A: SCHEDULE OF PROCEDURES

Visit	Screening	Baseline	Week 2	Week 4	Week 8	Week 12/ Early Term	Week 16 (Follow-Up)
Study Day [Window (days)]	**-14 to -1**	**1**	**14 [±3]**	**28 [±3]**	**56 [±3]**	**84 [±3]**	**112 [±3]**
Informed consent	X						
Demographics and medical history	X						
Eligibility assessment	X	X					
Diet and lifestyle counseling	X						
Randomization		X					
Vital signs	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Height (and BMI calculation)	X		X	X	X		
ECG	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X
Physical examination [1]	X	X	X	X	X	X	X
Chemistry [2]	X	X	X	X	X	X	X
Pregnancy test (female patients only)	X	X [3]	X	X	X	X	X
Coagulation panel	X	X [4]				X	
Urinalysis	X	X				X	
Thyroid function test [5]	X[6]	X	X	X	X	X	X
Lipid panel, apolipoproteins, ApoCIII, lipoprotein(a)	X[7]	X	X	X	X	X	X
Lipoprotein particle analysis		X				X	X
LDL-C by ultracentrifugation		X				X	
[redacted]	X	X	X	X	X	X	X
FSH, total and free testosterone [8], LH, CKMB, troponin I, reverse T3, ALP isoenzymes, P1NP, CTX, fibrinogen		X				X	X
HbA1c	X	X			X	X	

Footnotes on the next page.

APPENDIX A: SCHEDULE OF PROCEDURES (CONTINUED)

Visit	Screening	Baseline	Week 2	Week 4	Week 8	Week 12/ Early Term	Week 16 (Follow-Up)
Study Day [Window (days)]	**-14 to 1**	**1**	**14 [±3]**	**28 [±3]**	**56 [±3]**	**84 [±3]**	**112 [±3]**
Hepatitis panel [9] and HIV	X						
Backup sample		X				X	
Genomic samples		X					
PK sampling [10]		X	X[11]	X	X	X	
Urine drug screen	X						
[redacted]		X				X	
Fasting prior to visit [12] and Record time of statin dose		X	X	X	X	X	
Study drug dispensing and accountability by IRT[13]		X	X	X	X	X	
Review adverse events		X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X

1. A complete physical examination will be performed at screening. Targeted, symptom-directed physical examinations will be performed at all other study visits.
2. Includes calcium, phosphorus, GGT, CPK, and albumin. See Appendix B for a complete list of analytes.
3. Urine test for human chorionic gonadotropin at randomization.
4. Only PT and aPTT at baseline.
5. Includes TBG, TSH, total T3 and T4, and free T3 and T4 except for Screening (see footnote 6).
6. Exclude TBG.
7. Exclude ApoCIII.
8. Free testosterone will be calculated from total testosterone, [redacted], and serum albumin.
9. Includes hepatitis B, HBsAg, HCV, and HCVAb
10. Patients will be instructed not to take study drug prior to PK sampling except for Week 2 (see footnote 11).
11. Patients will fast and arrive at the study site in the morning and following a predose PK blood draw, be administered study drug. All other assessments will be performed except for ECG. At 4 hours post dose, a second blood draw for PK will be taken. Following the blood draw, patients may discontinue fasting. Patients will then rest for 30 minutes, after which an ECG will be performed.
12. Patients should fast for at least 10 hours prior to the visit.
13. Treatments include MGL-3196 100 mg, MGL-3196 60 mg, or placebo. Each patient will receive study drug bottles labeled as A and B. Patients will take 1 capsule from bottle A and 1 capsule from bottle B once daily in the morning. No study drug will be dispensed at Week 12 or Early Termination. Study drug accountability will not be assessed at baseline.

ALP = alkaline phosphatase; [redacted]; ApoCIII = apolipoprotein CIII; aPTT = activated partial thromboplastin time; BMI = body mass index; CKMB = creatine kinase MB; CPK = creatine phosphokinase; CTX = C-terminal telopeptide; ECG = electrocardiogram; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; [redacted]; IRT = Interactive Response Technology; LDL-C = low-density lipoprotein cholesterol; LH = luteinizing hormone; P1NP = procollagen type 1 N-terminal propeptide; [redacted] PK = pharmacokinetic; PT = prothrombin time; [redacted]; T3 = triiodothyronine; T4 = thyroxine; Term = termination; TSH = thyroid stimulating hormone.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Direct bilirubin
Estimated glomerular filtration rate [1]	Gamma-glutamyl transferase
Glucose	Inorganic phosphorus
Lactate dehydrogenase	Lipase
Magnesium	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

1. Calculated using Modification of Diet in Renal Disease (MDRD) formula.

Standard Hematology Panel

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential	

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

Coagulation

Activated partial thromboplastin time	Prothrombin time
International normalized ratio	

Serology

Hepatitis B	Hepatitis B surface antigen
Hepatitis C	Hepatitis C virus antibodies
Human Immunodeficiency Virus	Hepatitis C virus RNA (only if HCV Ab positive)

Lipid Panel

- Total cholesterol
- High-density lipoprotein cholesterol
- Calculated low-density lipoprotein cholesterol
- Triglycerides
- Non-high-density lipoprotein cholesterol
- Low-density lipoprotein cholesterol by preparative ultracentrifugation (Baseline and Week 12 only)

Additional Parameters

- Apolipoprotein A1
- Apolipoprotein CIII
- Lipoprotein particle analysis
- Sex hormone-binding globulin
- Follicle-stimulating hormone
- Luteinizing hormone
- Troponin I
- Alkaline phosphatase isoenzymes
- Angiopoietin-like 3
- C-terminal telopeptide
- Calculated free testosterone
- Hemoglobin A1c
- Apolipoprotein B
- Total and free thyroxine
- Total and free triiodothyronine
- Thyroid stimulating hormone
- Thyroid Binding Globulin
- High-sensitivity C-reactive protein
- Total testosterone
- Creatine kinase MB
- Reverse triiodothyronine
- Proprotein convertase subtilisin/kexin type 9
- Fibrinogen
- Procollagen type 1 N-terminal propeptide

Other assessments

Serum pregnancy test (female patients only)

Urine test for drugs of abuse

Pharmacokinetic sample

Backup samples

Genomic sample

APPENDIX C: SIMON BROOME REGISTER DIAGNOSTIC CRITERIA FOR HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Definite familial hypercholesterolemia is defined as:

- Total-C >6.7 mmol/L (260 mg/dL) or LDL cholesterol above 4.0 mmol/L (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/L (290 mg/dL) or LDL cholesterol above 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment);

PLUS

- Tendon xanthomas in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt);

OR

- DNA-based evidence of an LDL receptor mutation or familial defective apo B-100,

Possible familial hypercholesterolemia is defined as:

- Total-C >6.7 mmol/L (260 mg/dL) or LDL cholesterol above 4.0 mmol/L (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/L (290 mg/dL) or LDL cholesterol above 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment),

And at least one of the following:

- Family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative; or
- Family history of raised cholesterols >7.5 mmol/L (290 mg/dL) in adult 1st or 2nd degree relative or >6.7 mmol/L (260 mg/dL) in child or sibling under 16 years of age.

Reference: DeMott K, Nherera L, Shaw EJ, et al. Clinical guidelines and evidence review for familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2008. Available at: https://www.nice.org.uk/guidance/cg71/evidence/full-guideline-appendix-f-241917811.

APPENDIX D: WHO CRITERIA (DUTCH LIPID NETWORK CLINICAL CRITERIA) FOR DIAGNOSIS OF HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia	
Family history	
First-degree relative with known premature (men <55 yrs, women <60 yrs) coronary and vascular disease, OR First-degree relative with known LDL-C level above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR Children aged less than 18 years with LDL-C level above the 95th percentile	2
Clinical history	
Patient with premature (men <55 yrs, women <60 yrs) coronary artery disease	2
Patient with premature (men <55 yrs, women <60 yrs) cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels	
LDL-C >= 330 mg/dL (≥8.5 mmol/L)	8
LDL-C 250 – 329 mg/dL (6.5–8.4 mmol/L)	5
LDL-C 190 – 249 mg/dL (5.0–6.4 mmol/L)	3
LDL-C 155 – 189 mg/dL (4.0–4.9 mmol/L)	1
DNA analysis	
Functional mutation in the LDLR, apo B or [redacted] gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite Familial Hypercholesterolemia	>8
Probable Familial Hypercholesterolemia	6-8
Possible Familial Hypercholesterolemia	3-5
Unlikely Familial Hypercholesterolemia	<3

Reference: Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478-3490a. Available at: http://eurheartj.oxfordjournals.org/content/early/2013/08/15/eurheartj.eht273.