Statistical Analysis Plan	
Official title:	A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 in Patients With Heterozygous Familial Hypercholesterolemia
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STATISTICAL ANALYSIS PLAN

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:

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SAP 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 reviewed and approved this statistical analysis plan.

Signature | Date

[redacted]

February 15, 2018, 10:00am

Sr. Director, Biostatistics
Medpace

[redacted]

February 15, 2018

[redacted]

Chief Medical Officer,
Executive Vice President R&D
Madrigal Pharmaceuticals, Inc.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ANGPTL3	Angiopoietin-like 3
Apo	Apolipoprotein
AST	Aspartate aminotransferase
BMI	Body mass index
CK	Creatine kinase
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
hsCRP	High-sensitivity C-reactive protein
ITT	Intent-to-Treat
LDL-C	Low-density lipoprotein cholesterol
LLN	Lower limit of normal
LOCF	Last observation carried forward
MMRMMedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	Mixed Model for Repeat Measures
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
SAE	Serious adverse event
SHBG	Sex hormone-binding globulin
T3	Triiodothyronine
T4	Thyroxine
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This document provides a description of the statistical methods and procedures to be implemented for the analyses of data from the study with protocol number MGL-3196-06. Any deviations from this Statistical Analysis Plan (SAP) will be documented in the final clinical study report.

2. STUDY OBJECTIVES AND STUDY DESIGN

2.1 Study Objectives

2.1.1 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 heterozygous familial hypercholesterolemia (HeFH).

2.1.2 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 (TC)/high-density lipoprotein cholesterol (HDL-C) ratio,
    - Triglycerides,
    - Lipoprotein(a),
    - ApoB/Apolipoprotein A1 (ApoA1) ratio, and
    - Lipoprotein particle assessment;
- 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 percent change from baseline in LDL-C; and
- To determine the effect of exposure to MGL-3196 on LDL-C lowering.

2.1.3 Exploratory Objectives

- [redacted]

- [redacted]

2.2 Study Design

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 (Protocol Appendix C) or World Health Organization (WHO)/Dutch Lipid Network (score >8; Protocol Appendix D).

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, adverse events (AEs), vital signs (oral temperature, pulse rate, respiratory rate, and seated blood pressure).

The placebo group remains the placebo group throughout the study. At the Week 2 visit, in addition to other labs described below, a pharmacokinetic (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 electrocardiogram (ECG) will be obtained at 4 hours postdose after the 4 hour 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 at 4 hours 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 phosphorous) and hematology will be assessed at all study visits; a 12-lead ECG will be performed at all study visits; and coagulation and urinalysis will be performed at screening, 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], assessed at all study visits. [redacted], Creatine kinase MB isoenzyme and troponin I, will be assessed at baseline and Weeks 2, 4, 8, 12 and 16. Follicle-stimulating hormone, total and free testosterone, luteinizing hormone, reverse T3, fibrinogen, alkaline phosphatase isoenzymes, procollagen type 1 N-terminal propeptide, and C-terminal telopeptide will be assessed at baseline, Week 12, and Week 16; free testosterone will be calculated from total testosterone, SHBG, 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 data 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.

The schedule of procedures can be found in Protocol Appendix A.

2.3 Study Endpoints

2.3.1 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) (Lp(a)), ApoB/ApoA1 ratio, Apolipoprotein CIII (ApoCIII), and lipoprotein particle assessment;
- Absolute change from baseline in LDL-C;
- Mean percent change from baseline in LDL-C for all patients on study drug (60-100 mg); and
- Mean percent change from baseline in LDL-C according to MGL-3196 exposure.

The exploratory efficacy parameters include the following:

- [redacted]
- [redacted]

2.3.2 Pharmacokinetics

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.

2.3.3 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.

3. STATISTICAL METHODOLOGY

3.1 Baseline, Endpoint, and Other Statistical Considerations

Baseline for all efficacy and safety variables will be defined as Baseline visit (Day 1). If the measurement at this visit is missing, the last measurement prior to the first dose of randomized study drug will be used.

Only lipids measured less than 2 days after the last dose of study drug are considered as a valid post-baseline lipid assessment.

Post-baseline lipid assessments will be assigned a visit number based on the date of assessment relative to the first dose of the double-blind study drug. Visit windows will be defined as the scheduled time from dosing date with a 7-day window (±7 days). Within a visit window, if a scheduled visit occurs, then the measurement from this scheduled visit will be used as the measurement for this visit window. If no scheduled visit occurs within a visit window, the last measurement within the window will be used. If no visits occur within a visit window, the measurement of this visit will be treated as missing.

Descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) will be used to summarize the continuous data. Discrete measures will be summarized using counts and percentages.

The summary and analysis of efficacy and safety data will be based on the MGL-3196 and placebo group. The primary efficacy and selected secondary endpoints will also be analyzed by MGL-3196 exposure level for the patients taking MGL-3196: higher exposure group and lower exposure group. The MGL-3196 exposure levels are determined by the plasma MGL-3196 concentration at Week 2 and later visits to represent the overall MGL-3196 exposure level for patients. That is, patients satisfies one of the following two conditions will be included in high exposure group: projected Week 2 AUC >5000 mg*h/L, or if Week 2 AUC <5000 but Week 4 predose >1.5ng/mL (if on 60mg). Another analysis will be based on the [redacted] level for the patients taking MGL-3196: higher increase (≥140%) and lower increase (<140%) in [redacted] from baseline to Week 12.

3.2 Analysis Populations

3.2.1 Intent-to-Treat Population and Modified Intent-to-Treat Population

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 is defined as identical to the Safety Population.

The modified intent-to-treat (mITT) population includes all patients who are randomized in the study, received at least 2 weeks of study drug, and have valid lipid measurement at Week 2 or later visits. The mITT Population will be used for all efficacy analyses.

3.2.2 Per Protocol Population

The Per Protocol Population will include all mITT patients who finish the Week 12 visit with valid LDL-C measurements, have sufficient treatment compliance, and do not have any major protocol deviations. The following will be evaluated for major deviations prior to unblinding of the treatment allocation:

- Patients who violated eligibility criteria;
- Patients who did not complete the study;
- Patients who were <80% compliant with study drug;
- Patients who took prohibited concomitant medications;
- Patients who were unblinded; and
- Patients who had other substantial protocol deviations that may impact the efficacy assessment.

The Per Protocol Population will be used to assess robustness of the primary efficacy analysis results.

3.2.3 Safety Population

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.

3.3 Patient Disposition

The reason given for each screen failure will be summarized and listed. Patient disposition will be provided for all randomized patients. The number and percentage of patients in each of the following disposition categories will be presented:

- Patients who are randomized,
- Patients who start study drug,
- Patients who complete the 12-week study drug,
- Patients who complete the study (Week 12), and
- Patients who withdraw from the study.

For randomized patients who withdraw from the study, the primary reason for the withdrawal will be listed and summarized.

The number of patients included in each analysis population will be summarized.

3.4 Demographics and Baseline Characteristics

Demographics (age, sex, race, and ethnicity), body weight, height, and body mass index (BMI) will be summarized by randomized treatment using descriptive statistics for the randomized patients based on the Safety Population. Age group (<65 years, or ≥65 years), BMI category (<25 kg/m^2, 25-30 kg/m^2, or >30 kg/m^2), statin category (Atorva 80 mg, Rosuva 20/40 mg, or No/Low Dose Statin), statin use (Atorvastatin, Rosuvastatin, Pravastatin, or None), Ezetimibe Use (Yes, or No), and undergoing PCSK9 inhibitor treatment (Yes, or No) will also be summarized.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with medical history will be summarized by their MedDRA preferred term within system organ class and by treatment.

3.5 Prior/Concomitant Medications

The use of any prior medication and concomitant medication will be listed for the Safety Population with an indication of whether the medication was prior or concomitant during the study.

Medications will be coded using the most recent version of World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking each concomitant medication will be summarized by preferred term within Anatomical Therapeutic Chemical classification and by treatment group for the Safety Population. A concomitant medication is defined as any medication taken on or after the first dose day of study medication.

3.6 Study Medication Exposure and Compliance

Days of exposure to study medication will be summarized by treatment group for the Safety Population using descriptive statistics. Exposure in days is defined as the date of last dose of study drug minus the date of first dose of study drug plus 1. In addition, a contingency table will be provided to display the number and percentage of patients with exposure in the following categories:

- 1 to ≤2 weeks (1-14 days),
- >2 to ≤4 weeks (15-28 days),
- >4 to ≤8 weeks (29-56 days),
- >8 to ≤12 weeks (57-84 days), and
- >12 weeks (85 days or more).

Compliance between Weeks 4 and 12 will be calculated based on the total actual number of capsules taken as compared to the total expected number of capsules taken (2 per day). Percent compliance with the study medication will be summarized by treatment group for the Safety Population using descriptive statistics. Additionally the number and percentage of patients within each treatment group with overall compliance in the following categories: <80%, 80% to 120%, and >120%, will be provided. Overall compliance will not be calculated.

Patients randomized to active study drug will be treated as follows: On the morning of Day 1, patients will receive MGL-3196 100 mg. At the Week 2 visit, patients will be administered one dose of MGL-3196 100 mg, and a 4 hour postdose MGL-3196 PK assessment will be made while patients are fasting. Patients will receive MGL-3196 60 mg between the Week 2

and Week 4 visits. At the Week 4 visit, patients will either continue to receive MGL-3196 60 mg or be placed back on 100 mg depending on their Week 2 MGL-3196 level at 4 hours 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.) The duration of each dose level will be summarized and number/percentage of patients taking each dose at each visit will be tabulated.

3.7 Analysis of Efficacy

3.7.1 Descriptive Statistics

All available raw and derived data will be listed for the randomized patients. Descriptive statistics for baseline, change from baseline or percent change from baseline to each post-baseline visit will be presented by treatment group for each efficacy measurement for the mITT Population.

3.7.2 Primary Efficacy Analyses of LDL-C

The primary efficacy variable will be the percent 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 and percent change from baseline will be provided.

The primary efficacy variable, the percent change in LDL-C from baseline to Week 12, will be analyzed using an analysis of variance (ANOVA) model with treatment (MGL-3196 or placebo) as a factor based on the mITT population. For any patients in the mITT Population with a missing primary efficacy variable, the last post-baseline observation carried forward (LOCF) method will be used. The least-squares mean, 95% confidence interval, and p-value will be provided for the comparison of MGL-3196 versus placebo.

Sample SAS® code is provided below:

```
*****************************************************************
** PCHG = Percent change in LDL-C from Baseline to Week 12      **
** TRT = Treatment group where 0 = placebo, 1= MGL-3196         **
*****************************************************************
PROC GLM;
   CLASS TRT;
   MODEL PCHG = TRT;
   LSMEANS TRT / e pdiff=control("0") cl;
RUN;
```

In addition to the percent change from baseline to Week 12 in LDL-C, the change in LDL-C from baseline to Week 12 will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and the baseline value as a covariate. For any patients in the mITT Population with a missing primary efficacy variable, the LOCF method will also be used.

Sample SAS® code is provided below:

```
*****************************************************************
** CHG = Change in LDL-C from Baseline to Week 12               **
** TRT = Treatment group where 0 = placebo, 1= MGL-3196         **
** BASE = Baseline LDL-C                                        **
*****************************************************************
PROC GLM;
```

```
    CLASS TRT;
    MODEL CHG = TRT BASE;
    LSMEANS TRT / e pdiff=control("0") cl;
RUN;
```

The same analysis models for Week 12 LDL-C are also used to analyse the percent change and change in LDL-C from baseline at Week 2 and Week 4 LOCF.

The primary efficacy analysis will be performed based on the Per Protocol Population to evaluate the robustness of the primary efficacy analysis.

Other imputation method for missing values of Week 12 LDL-C will be evaluated, including multiple imputation and Mixed Model for Repeated Measurements (MMRM) method based on the mITT population. The multiple imputation method will use statin group (80 mg Atorvastatin, 20/40 mg Rosuvastatin, or No/Low Dose Statin), baseline and all the post-baseline valid LDL-C values as references for the imputation with the monotone missingness assumption. The MMRM method will include treatment and visit as factors, and treatment by visit interaction.

3.7.3 Subgroup Analysis of LDL-C

The subgroup analysis of LDL-C will be based on the mITT population. Since the analyses are for descriptive purposes only, no adjustments will be made for multiplicity.

The analysis of LDL-C will be performed based on MGL-3196 exposure group. In the analysis of LDL-C based on MGL-3196 exposure group, the patients who are taking MGL-3196 will be categorized into higher and lower exposure groups. The same ANOVA and ANCOVA models will be used, with pairwise comparisons between each exposure group versus placebo will be provided.

The analysis of LDL-C will also be performed based on SHBG group. In the analysis of LDL-C based on SHBG group, the patients who are taking MGL-3196 will be categorized into groups with higher increase or lower increase of SHBG from baseline to Week 12. Patients who are taking MGL-3196 but do not have Week 12 SHBG values will not be included. The same ANOVA and ANCOVA models will be used, with pairwise comparisons between each exposure group versus placebo to be provided.

The final dose of MGL-3196 (100 mg or 60 mg) will also be used to repeat the primary efficacy analysis. Similar to the exposure group, an analysis will be performed, but with the final dose of MGL-3196 to categorize patients who are taking MGL-3196.

The primary efficacy analysis of LDL-C will be repeated based on the following subgroups:

- Statin subgroup (80 mg Atorvastatin, 20/40 mg Rosuvastatin, or No/Low Dose Statin);
- Exposure group, SHBG group, in combination with statin subgroup;
- Gender subgroup (male, or female);
- Exposure group, SHBG group, in combination with gender subgroup;
- Baseline LDL-C value (<100 mg/dL, or ≥100 mg/dL);
- Statin and baseline LDL-C subgroup;

- Exposure group, SHBG group, Final MGL-3196 dose group, in combination with baseline LDL-C subgroup;
- Baseline BMI value (<25 kg/m^2, or ≥25 kg/m^2; and <30kg/m^2, or ≥30 kg/m^2);
- Exposure group, SHBG group, Final MGL-3196 dose group, in combination with baseline BMI subgroup;
- Average TSH between baseline and screening subgroup (<2 mIU/L, or ≥2 mIU/L);
- Exposure group, SHBG group, Final MGL-3196 dose group, in combination with average TSH between baseline and screening subgroup;

3.7.4 Secondary Analysis of LDL-C

The following treatment targets will be explored:

- Reaching LDL-C at Week 12 LOCF <100 mg/dL. Patients who have cardiovascular disease will be excluded from this analysis.
- Reaching LDL-C at Week 12 LOCF <70 mg/dL.
- Reaching LDL-C target endpoint at Week 12: For patients who have cardiovascular disease, the target endpoint is <70 mg/dL; and for all other patients the target endpoint is <100 mg/dL.

For the analysis reaching LDL-C <100 mg/dL, <70 mg/dL, or the target endpoint at Week 12 LOCF, a logistic regression model with treatment as a factor and baseline LDL-C as a covariate will be used. The odds ratio, confidence intervals and p-values from the logistic regression analysis will be presented for the treatment difference between MGL-3196 and placebo.

Sample SAS® code for logistic regression is provided below:

```
*****************************************************************
** ANL01FL = Reaching treatment goal, where 1=Yes 0=No          **
** TRT = Treatment group where 0 = placebo, 1= MGL-3196         **
** BASE = Baseline LDL-C                                       **
*****************************************************************
PROC GENMOD DESCENDING;
   CLASS TRT;
   MODEL ANL01FL = TRT BASE / d=b link=logit;
   ESTIMATE "MGL3196 vs Placebo" TRT -1 1;
RUN;
```

It is observed that the screening values and baseline values of LDL-C have relatively high variation. Therefore, the change from screening to Week 12 LOCF in LDL-C will also be explored.

Due to the variation between screening and baseline values of LDL-C, it is expected that some patients will have baseline LDL-C <100 mg/dL. Therefore, more exploratory analysis of reaching LDL-C treatment goals at Week 12 based on patients with baseline LDL-C ≥100 mg/dL only may be conducted.

3.7.5 Secondary and Exploratory Endpoint Analyses

All the secondary and exploratory endpoints will be summarized and analyzed based on the mITT Population. In addition to the overall analysis, analyses by exposure group, [redacted] group, and final study drug dose will also be performed. No adjustments will be made for multiplicity.

For continuous variables, the ANCOVA model specified for the primary analysis will be used. For patients with missing values at Week 12, the LOCF method will be used for imputation. Normality will be tested for the model residuals.

For Lp(a), statin subgroup and baseline Lp(a) subgroup (≤10 or >10 nmol/L) will be summarized and analyzed, as well as other cut-offs (70 nmol/L) and quartile analyses as appropriate. The statin subgroup will also be explored for ApoB, ApoCIII, and other lipids if appropriate. Other subgroup analysis will also be conducted as needed.

For triglycerides and [redacted], a logarithm transformation may be performed prior to fitting the ANCOVA model for change in triglycerides and [redacted]. The treatment comparisons will be transformed back to the difference in percent change from baseline. If the model residuals for the ANCOVA model of the logarithm transformed data still do not satisfy the normality assumption, the Wilcoxon rank-sum test will be performed as the main analysis to compare the percent change from baseline to Week 12. In addition to the Wilcoxon rank-sum test, the Hodges-Lehmann method will be used to estimate the median difference and its corresponding 95% confidence interval.

For certain efficacy endpoints, the MMRM method may be used to test the robustness of the results with treatment and visit as factors, and treatment by visit interaction. The treatment difference at Week 12 will be estimated from the MMRM.

For categorical variables, Fisher's exact test will be used to compare the percentages between MGL-3196 doses versus placebo at each post-baseline visit.

3.8 Analysis of Safety

The safety endpoints for this study include: AEs, safety laboratory assessments, vital signs, 12-lead ECGs, physical examinations, and clinical assessments. The safety endpoints will be summarized based on the Safety Population.

3.8.1 Adverse Events

Treatment-Emergent Adverse Events (TEAEs) are defined as adverse events that are new or worsen after the first dose of study drug. AE worsening applies to severity or relationship to study drug.

A summary overview of TEAEs will be provided, which presents the number and percentage of patients in each treatment group from the Safety Population satisfying each of the following categories:

- Any TEAEs,
- Maximum severity of TEAEs,
- Study drug-related TEAEs,
- Maximum severity of study drug-related TEAEs,
- All treatment-emergent serious adverse events (SAEs),
- All study drug-related TE-SAEs,
- TEAEs leading to death,
- TEAEs leading to study drug discontinuation, and
- Study drug-related TEAEs leading to study drug discontinuation.

Adverse events will be coded using MedDRA. The number and percentage of patients with TEAEs will be summarized by their MedDRA preferred term within system organ class and by treatment. AEs will be counted by the number of events as well as the number of patients. For event count summaries, multiple AE events with the same MedDRA coded terms (preferred term and system organ class) and onset date and time from the same patient will only be counted once. For patient count summaries, multiple AE events with the same MedDRA coded terms (preferred term and system organ class) from the same patient will only be counted once.

The number and percentage of patients with TEAEs will be summarized by reported maximum severity within each MedDRA preferred term within system organ class and by treatment.

The number and percentage of patients with TE-SAEs, any drug-related TEAEs, drug-related TE-SAEs, and TEAEs and TE-SAEs that lead to study drug discontinuation will be summarized by preferred term within system organ class and by treatment. In these summaries, any patients reporting multiple episodes of the same TEAE (i.e., same preferred term and system organ class) will be counted once.

All SAEs will be listed with an indication of whether the SAE was treatment emergent or started prior to treatment.

All TEAEs that are reported as leading to study drug discontinuation will be listed.

3.8.2 Clinical Laboratory Assessments

3.8.2.1 Chemistry and Hematology

Descriptive statistics of each chemistry and hematology parameter will be presented for baseline values and for values and changes from baseline at each post-baseline visit. These will be presented by treatment group for each parameter using the Safety Population.

Counts and percentages of patients with any post-baseline observation that is below the lower limit of normal (<LLN) or above the upper limit of normal (>ULN) will be summarized for each chemistry and hematology parameter by treatment group and overall.

The liver enzyme parameters (ALT, AST, creatine kinase [CK], and GGT) will be analyzed for the overall Safety Population by active and placeobo groups, and by exposure group, final dose group, and SHBG group. Statin subgroup will also be explored. Patients with mild liver diseases will not be included in the analysis of liver enzyme parameters, since the liver enzyme value will be affected. The possible liver disease may include, but is not limited to: elevated

liver enzymes (elevated direct bilirubin ≥0.3 mg/dL, or GGT > 100 U/L) or large amount of alcohol use.

The shift from baseline value to the worst post-baseline value will be summarized for selected parameters (AST, ALT, total bilirubin, alkaline phosphatase, creatinine, and CK). Shift categories will be based on normal ranges (<LLN, Normal, >ULN).

3.8.3 12-Lead Electrocardiogram

ECG parameters (heart rate, PR interval, QRS interval, QT interval, QTcB interval, QTcF interval, RR Interval, and overall interpretation) will be summarized by treatment group using descriptive statistics for the Safety Population. The average of 3 readings will be used in the summaries. For the overall interpretation, the most severe interpretation at the visit will be summarized. The count and percentage of patients with QTcF and/or QTcB above thresholds (>450 msec, >480 msec, >500 msec) or change from baseline above thresholds (>30 msec, >60 msec) will be summarized by treatment group for the Safety Population.

3.8.4 Physical Examination

The number and percentage of patients with abnormal physical examination findings will be presented for the Safety Population.

3.8.5 Vital Signs, Weight, Height, BMI

Vital signs parameters will be summarized using descriptive statistics for the Safety Population. The change from baseline will also be presented.

3.8.6 Other Safety Parameters

Other safety data will be listed.

3.9 Pharmacokinetic Analysis

Blood samples for PK assessments will be obtained pre-dose from patients at the Baseline Visit (Day 1), and at Weeks 2, 8, and 12, and the Early Termination Visit. Blood samples for PK assessments will also be obtained 4 hours post-dose at Week 2 to inform the MGL-3196 dosing starting at Week 4. Statin PK will be assessed at baseline and Week 2 and may be assessed at later visits as well.

PK concentrations will be summarized descriptively.

Concentration of statins and PK concentration of MGL-3196 will be assessed to determine any drug interactions or relationship to safety.

3.10 Interim Analysis

There is no planned interim analysis for this study.

4. SAMPLE SIZE DETERMINATION

Up to 105 patients in total will be randomized to 1 of 2 treatments (70 patients 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 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.

5. PROGRAMMING SPECIFICATIONS

Statistical analyses will be performed using SAS® (Cary, NC) version 9.3 or above. All available data will be presented in patient data listings, which will be sorted by site number, unique patient identifier and where appropriate, visit number and visit/assessment date.

The programming specifications, including mock-up validity listings, analysis tables, figures, and data listings, as well as the derived database specification, will be prepared in stand-alone documents.