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

NCT ID: NCT02722408

Approval Date: 07-Jun-2017

APPENDIX 16.1.9: DOCUMENTATION OF STATISTICAL METHODS

MEDPACE
THE ADVANTAGE OF FOCUS

STATISTICAL ANALYSIS PLAN

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

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

Sponsor:
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Version Number: 1.0
Date: 7 June 2017

SIGNATURE PAGE

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Protocol Number: GEM-201

We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

Signature	Date
PI [redacted]	12 June 2017
[redacted]	12 June 2017
[redacted]	12 JUN2017
PI [redacted]	12 June 2017

Gemphire Therapeutics Inc.

VERSION HISTORY

Version	Date	Description
1.0	07 June 2017	Original signed version

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LIST OF ABBREVIATIONS

Apo	Apolipoprotein
ATC	Anatomical Therapeutic Chemical
AUC_{0-24}	Area under the concentration-time curve to the 24-hour time point
AUC_{0-t}	Area under the concentration-time curve to the last quantifiable time
C_{max}	Maximum plasma concentration
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
FAS	Full Analysis Set
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolemia
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Affairs
non-HDL-C	Non-high-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
QD	Once daily
RTF	Rich Text Format
SAE	Serious adverse event

SAP	Statistical Analysis Plan
SP	Safety Population
SOP	Standard Operating Procedure
TC	Total cholesterol
TG	Triglyceride
t_{max}	Time to maximum plasma concentration
TSH	Thyroid-stimulating hormone
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

1 INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from Gemphire Therapeutics Inc. ("Gemphire"), Clinical Trial Protocol GEM-201. This document is based on protocol version 1.0 dated February 19, 2016. If circumstances arise during the study such that more appropriate analytic procedures become available, the statistical analysis plan (SAP) may be revised. Any revisions to the SAP (both alternative and additional methods) will be made prior to database lock and reasons for such revisions will be described in the final Clinical Study Report (CSR).

2 OVERVIEW

2.1 Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

The secondary objectives are the following:

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

2.1.3 Exploratory Objective

CI [redacted]

2.2 Trial Design

This is a Phase 2, open-label, dose-finding, 3-period, 3-treatment study using successively escalating doses of 300 mg, 600 mg, and 900 mg gemcabene in patients with HoFH. All patients will be on each of the successive doses for 4 weeks at a time. Patients will remain on their current

stable, lipid-lowering therapy throughout the study. Patients will not be allowed in the study if they are undergoing apheresis or taking mipomersen or lomitapide.

The population for this study is male and female patients, ≥17 years of age, diagnosed with HoFH by genetic confirmation or a clinical diagnosis based on either (1) a history of an untreated LDL-C concentration >500 mg/dL (12.92 mmol/L) together with either appearance of xanthoma before 10 years of age, or evidence of heterozygous familial hypercholesterolemia in both parents or, if history is unavailable, (2) LDL-C >300 mg/dL (7.76 mmol/L) on maximally tolerated lipid-lowering drug therapy. Approximately 8 patients will be enrolled into the study. Total study duration will be up to 18 weeks and will consist of a Screening Visit, a Treatment Period, and a Follow-up Visit.

The Treatment Period is a sequential design whereby each patient will receive gemcabene 300 mg QD for 4 weeks. The same patients will then receive a 600 mg dose QD for 4 weeks and finally 900 mg dose QD for 4 weeks. There will be no interruptions in gemcabene dosing when changing from the 300 mg to the 600 mg dose or when changing from the 600 mg to the 900 mg dose unless there are clinically significant safety issues resulting in the temporary or permanent discontinuation of study drug. The first 300 mg dose of study drug will be administered at the site on Day 1. Assessments will be performed after the patient has been on the study drug for 2 weeks for each dosing level and on the last day of each dose.

The Follow-up Visit will occur 4 weeks (±3 days) after the last dose of study drug.

The schedule of events for the trial is provided in Table 1.

Table 1. SCHEDULE OF PROCEDURES

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

Footnotes appear on the following page

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

Apo = apolipoprotein; ECG = electrocardiogram; eCRF = electronic Case Report Form; ET = Early Termination; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; K_2EDTA = dipotassium ethylenediaminetetraacetic acid; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); NCEP ATP-III = National Cholesterol Education

Program Adult Treatment Panel III; NGAL = neutrophil gelatinase-associated lipocalin; non-HDL-C = non-high-density lipoprotein; [redacted] PK = pharmacokinetic; TC = total cholesterol; TG = triglyceride; TSH = thyroid-stimulating hormone; VLDL-C = very low-density lipoprotein cholesterol.

3 ANALYSIS VARIABLES

3.1 Efficacy Variables

3.1.1 Primary efficacy variable

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

3.1.2 Secondary efficacy variables

The secondary efficacy analyses are the following:

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

3.1.3 Exploratory efficacy variables

CI [redacted]

3.2 Safety Variables

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

3.2.1 Adverse Events

AEs will be assessed at all study visits and the Follow-up Visit. Adverse events that occur on or after the first dose of study drug (Day 1) will be considered treatment-emergent adverse events (TEAEs). Further details regarding AEs, such as the definition of an AE or serious adverse event (SAE), TEAEs, assessment of severity, assessment of causality, etc., are described in Section 9.1 and 9.2 of the protocol.

3.2.2 Safety Laboratory Evaluations

Standard clinical laboratory evaluations for safety chemistry, coagulation, hematology, and urinalysis will be conducted at all study visits and the Follow-up Visit (only for patients who had an abnormal result at Day 84 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event). Clinically significant abnormal creatinine results at Day 84 (or the ET Visit, if applicable) will also be followed-up 2 weeks (±3 days) after the last dose of study drug in addition to the 4 week (±3 days) Follow-up Visit.

3.2.3 Vital Signs

Measurement of vital signs will include an assessment of pulse rate, blood pressure, respiration rate, and temperature. Vital signs will be measured at all study visits, excluding the Follow-up Visit.

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

3.2.4 Electrocardiograms

ECGs will be performed in triplicate and sent to a central reviewer. A 12-lead ECG will be performed at the Screening Visit and pre-dose on Day 1, Day 14, Day 42, Day 70, and the ET Visit, if applicable. Electrocardiograms will be performed pre-dose and 2 hours post-dose on Day 28, Day 56, and Day 84.

3.2.5 Physical Examinations

A full PE will be performed at the Screening Visit, Day 84, and the ET Visit, if applicable, and includes genitourinary examination per the Investigator's discretion and does not include a rectal examination. Assessment for xanthoma or arcus should also be part of the full PE.

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

3.3 Pharmacokinetic Variables

3.3.1 Concentration Data

Pharmacokinetic samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose) and 0.5, 1, 2, 3, 5, and 12 hours post-dose on Day 28, Day 56, and Day 84 in collection tubes containing K_2EDTA as the anticoagulant. For all other study visits where routine plasma drug monitoring will be performed (Day 1, Day 14, Day 42, Day 70, and the ET Visit, if applicable), samples will be collected pre-dose (must be 24 ±2 hours from the previous day's dose if a previous day's dose occurred).

3.3.2 Pharmacokinetic Parameters

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

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

4 ANALYSIS POPULATIONS

Two analysis populations are designed for the study: the Full Analysis Set (FAS) Population and the Safety Population (SP).

4.1.1 Safety Population

The SP will include all patients who are enrolled into the study and have at least 1 dose of study drug. This population will be used to summarize all safety data.

4.1.2 Full Analysis Set Population

The FAS will include patients from the Safety Population who also have a valid post-baseline efficacy assessment, for a given dose level.

5 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

PI is responsible for the statistical analyses for this trial. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant International Conference of Harmonisation (ICH)-E9 guidelines and PI biostatistical standard operating procedures (SOPs). All tables, figures, and listings will be generated with SAS® (SAS Institute Inc., Cary, North Carolina, USA) Version 9.3 or higher and printed using a Rich Text Format (RTF) file format.

5.1 Evaluation of Center Effect

Due to the design, objectives, and sample size of the trial, center effects will not be evaluated.

5.2 Assessment Windows

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

For analysis purposes, if the event date is on or after the first treatment date, the study day is defined as follows:

$$\text{Study Day} = \text{Event date} - \text{First treatment date} + 1$$

Therefore, the day of first treatment will be Day 1. If the event date is prior to the first treatment date, the addition of 1 will not be included in the calculation; thus, there will be no Day 0.

5.3 Handling of Dropouts and Missing Data

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

Adverse events with missing start dates will be considered as treatment-emergent unless the partial date excludes that possibility, e.g. the adverse event month is prior to the treatment infusion month. Otherwise, the first day of the month will be used to impute missing start days and January will be used to impute missing start months.

5.4 Programming Specifications

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

6 ANALYSIS OF DISPOSITION AND SUBJECT CHARACTERISTICS

6.1 Disposition and Analysis Populations

Subject disposition information will be summarized. Counts (number and percent) of subjects who are randomized, who are dosed with study medication, who complete the study, and who withdraw early from the study will be presented. The primary reasons for early withdrawals will

also be tabulated. The SP will be used as the denominator for the percentage calculation. Subject disposition, inclusion / exclusion criteria and comments will be listed.

The number and percent of patients in each analysis population will also be tabulated.

6.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the Safety population and for FAS population, if it differs from the SP.

Demographic and baseline characteristics include, but are not limited to, age at informed consent, gender, race, ethnicity, height, baseline weight, and baseline body mass index. Continuous variables (e.g., age, weight, etc.) will be summarized by descriptive statistics. Categorical variables (e.g., gender, race, and ethnicity) will be summarized by the number and percentage of patients in corresponding categories. Demographic characteristics will also be listed.

Medical/surgical history will be summarized for the number and percentage of patients for each system organ class and preferred term. Medical history will also be listed.

Genetic testing results for the HoFH genotype mutational status will be listed by patient.

6.3 Concomitant Medications

All medications administered during the study will be listed and coded using the most current version of the World Health Organization (WHO) Drug Reference List. A listing of all prior and concomitant medications including the reported term, preferred term, and Anatomical Therapeutic Chemical (ATC) class, start and stop dates, and other relevant data will be provided for the SP. Concomitant medications include all medications taken on or after the date of the first dose of study drug. Prior medications include all medications taken before the date of the first dose of study drug and discontinued before the first dose of study drug.

7 ANALYSIS OF EFFICACY

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

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

Given the proposed crossover design of this study, a within-patient analysis can be performed for the comparison of dose groups. For continuous variables, the dose groups will be compared on their change and percent reduction from baseline (using their pre-treatment baseline value). For binary variables such as the percentage of patients, descriptive statistics will be calculated for each dose group.

Baseline lipid measurements will be defined as the average of the last two fasting measurements prior to the first dose of study medication. If only one measurement is available then this measurement will be used as baseline. Baseline for all other efficacy variables will be the last measurement prior to the first dose of study medication.

7.1 Primary Efficacy Analysis

Descriptive statistics of the percent change from baseline in LDL-C will be presented by treatment group at each visit, with the focus being on the percent change from baseline to Day 28, Day 56, and Day 84 in LDL-C, using the FAS. A longitudinal analysis will be performed with a mixed-effects model repeated measures analysis including percent change in LDL-C as the dependent variable, visit as a fixed effect and patient as a random effect. The additional drug benefit with increasing dose will be estimated from the mixed-effects model. The FAS will be used for this analysis. Least-squares mean differences and corresponding 95% confidence intervals, separately for each of the 3 paired comparisons (300 versus 600 mg, 300 versus 900 mg, and 600 versus 900 mg) will be provided.

The mixed-effect model repeated measures analysis will use an unstructured covariance matrix for the within-subject correlation; if the model does not converge with this correlation structure, an auto-regressive correlation structure will be assumed. If the model still does not converge then other covariance structures will be explored. The final correlation structure will be determined by the information criteria of Akaike and Schwarz. The data from each scheduled visit will be included in the model. Example SAS® code for performing this analysis is as follows:

```
PROC MIXED;
  CLASS SUBJID VISIT;
  MODEL PCHG = VISIT;
  REPEATED VISIT / type=UN subject=SUBJID;
  LSMEANS VISIT / cl pdiff;
RUN;
```

In addition, a scatterplot with a linear regression fit of the percent reduction from baseline versus dose will be performed.

7.2 Secondary Efficacy Analyses

Similar summaries and analyses will be carried out for the continuous secondary efficacy variables, assessing change from baseline and percent change from baseline in LDL-C (change from basline only), non-HDL-C, TC, TG, HDL-C, VLDL-C, ApoB, ApoA-I, ApoA-II, ApoC-II, ApoC-III, ApoE, Lp(a), hsCRP, and fibrinogen at each scheduled time point. Sub-group analyses

will be performed for LDL-C, non-HDL-C, TC, TG, HDL-C, and VLDL-C, according to receptor mutation status. The FAS will also be used for the summary and analysis of the secondary efficacy endpoints.

Descriptive statistics, including the count and percentage, will be obtained for patients achieving LDL-C reduction of ≥15%, ≥20%, ≥25%, and ≥30% at each visit, with the focus being on Day 28, Day 56, and Day 84 using the FAS. Similar analyses will be obtained for patients achieving an LDL-C value <100 mg/dL (2.59 mmol/L) at Day 28, Day 56, Day 84, and at any time during the study.

7.3 Exploratory Efficacy Analyses

CI [redacted]

8 ANALYSIS OF SAFETY

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

8.1 Extent of Exposure

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

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

Days of exposure to study drug will be summarized with descriptive statistics by treatment group for the Safety population.

Days of possible exposure, within a given dose level, is defined as the date of last dose of study drug minus the date of first dose of study drug plus 1. When the last known dose date is missing, the last known clinic visit date will be used.

Percent compliance with the study drug will be summarized by treatment group for the SP using descriptive statistics. Within a given dose level, compliance will be calculated by the total number of tablets taken divided by the total number of tablets presumed taken during the treatment period times 100. The total number of tablets taken is calculated by the total number of tablets dispensed minus the total number of tablets returned. The total number of tablets presumed taken is calculated by the number of days during the treatment period times the number of tables scheduled to be taken daily for the treatment period (i.e. 1 tablet for 300 mg period, 2 tables for the 600 mg period, and 3 tables for the 900 mg period).

The analysis will include listings for drug exposure and compliance.

8.2 Adverse Events

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

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

- All TEAEs,
- Drug-related TEAEs,
- Maximum severity of TEAEs,
- Maximum severity of drug-related TEAEs,
- All treatment-emergent SAEs,
- Drug-related treatment-emergent SAEs,
- Death due to TEAEs,
- TEAEs leading to study drug discontinuation, and
- Drug-related TEAEs leading to study drug discontinuation.

The numbers and percentages of patients with TEAEs will be summarized by MedDRA preferred term within system organ class, by treatment group and overall. For the summaries by treatment group, multiple AEs with the same MedDRA preferred term within system organ class from the same patient within a given treatment will only be counted once. For overall summaries, multiple AEs with the same MedDRA preferred term within system organ class from the same patient will only be counted once. The AE onset date will determine the treatment group classification for the AE.

All TEAEs related to study drug, SAEs, and AEs leading to study drug discontinuation will be summarized in the same manner. Summaries will also be provided for the numbers and percentages of patients by system organ class, preferred term, and maximum severity, for TEAEs and drug-related TEAEs.

All AEs will be included in by-patient listings containing additional information of interest such as onset and resolution times, maximum severity, causal relationship to study medication, and action taken. Specific by-patient listings of SAEs and TEAEs leading to study discontinuation will be provided.

8.3 Safety Laboratory Parameters

Clinical chemistry, coagulation, hematology, and urinalysis results will be summarized with descriptive statistics at all visits with the focus on Day 28, Day 56, and Day 84. Change from baseline will also be summarized. Frequency counts of new or worsening abnormalities will also be provided. Laboratory values will also be listed by visit, within patient.

8.4 Vital Signs

Vital signs and the change from baseline will be summarized descriptively by visit. Vital sign data will also be listed by visit, within patient.

8.5 ECG Parameters

Electrocardiogram results will be summarized with counts and percentages by visit and results will also be listed.

8.6 Physical Examinations

Physical examinations at baseline and the change from baseline will be summarized by visit. Physical examination results will also be listed by visit, within patient.

8.7 Pharmacokinetic Analysis

A separate Pharmacokinetic Analysis Plan will be prepared by Gemphire describing the details regarding the PK analysis, including the data handling and methods for the analysis. Gemphire will perform the PK analysis and generate the corresponding PK Report which will be included as an appendix to the CSR.

9 DATA SAFETY MONITORING BOARD

Not applicable.

10 INTERIM ANALYSIS

Interim analysis #1 occurred based on study data through a cut-off date of January 12, 2017. The purpose of this interim analysis was to provide preliminary efficacy and safety information to Gemphire and prospective partners. The timeframe includes data through Week 12 for subject PI , through Week 12 for subject PI and through Week 8 for subject PI based on source data that was monitored and checked for quality control. The interim analysis included the following information:

- Patient demographics and exposure
- Genetic analysis of HoFH status
- Primary efficacy parameter of LDL-C
- Adverse events

Interim analysis #2 will occur based on study data through a cut-off date corresponding to the last subject's Week 12 visit. The purpose of this interim analysis is to provide preliminary efficacy and safety information to Gemphire and prospective partners. The timeframe includes data through Week xxx for subjects xxxx based on source data that is monitored and checked for quality control. The interim analysis includes the following information:

- Patient demographics, exposure, and concomitant lipid medications
- Genetic analysis of HoFH status
- Primary efficacy parameter of LDL-C
- Summary of LDL-C by receptor mutation status (HoFH status)
- Adverse events

11 SAMPLE SIZE AND POWER CONSIDERATIONS

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

12 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

It was decided that the Intent-to-Treat (ITT) population defined in the protocol will be renamed as the FAS for the analysis. No changes were made to the statistical methodology described in the protocol.

13 REFERENCES

None