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

NCT ID: NCT02634151

Approval Date: 10-Jul-2017

Statistical Analysis Plan: GEM-301

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

Study Number: GEM-301

Study Phase: Phase 2

Sponsor: Gemphire Therapeutics Inc.
17199 N. Laurel Park Drive, Suite 401
Livonia, Michigan 48152
United States
Telephone: +1-248-681-9815
Facsimile: +1-734-864-5765

Version: Amendment 1.0

Date: 10 Jul 2017

Revision History

Version	Date	Revision Author	Comments
Amendment 1.0	10 July 2017	PI	See Document History for summary of changes

Confidentiality Statement

1 TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

2 SIGNATURE PAGE

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

Study Number: GEM-301

Prepared by:	PI PI	
Reviewed by:	PI PI .	
Approved by:	PI Gemphire Therapeutics Inc.	
Approved by:	PI Gemphire Therapeutics Inc.	

PI

Document History – Major changes compared to previous versions of the analysis plan

Version	Date	Changes
Final 1.0	17-Apr-17	N/A
Amendment 1.0	10-Jul-17	Added that potentially clinically significant laboratory values, single occurrences, will also be summarized by statin-intensity stratum. Added information on imputing drug interruptions with partial start/stop dates to be 1 day in length along with technical comments regarding assignment. Added that we are summarizing days on treatment and days drug was interrupted for. Added 2 urinalysis parameters to PCS criteria. Updated PPS section. Edited text to reflect hsCRP and TG being analyzed using ranked ANCOVA.

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE	angiotensin-converting enzyme
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Apo	apolipoprotein
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
BUN	blood urea nitrogen
CFBL	change from baseline
CI	confidence interval
CRF	case report form
CVD	cardiovascular disease
DBP	diastolic blood pressure
DPP	dipeptidyl peptidase
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FAS	Full Analysis Set
FPG	fasting plasma glucose
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HoFH	homozygous familial hypercholesterolemia

hsCRP	high-sensitivity C-reactive protein
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
Lp(a)	Lipoprotein(a)
LSM	least-squares mean
MAO	monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
NCEP ATP-III	National Cholesterol Education Program Adult Treatment Panel III
NGAL	neutrophil gelatinase-associated lipocalin
OR	odds ratio
PCS	potentially clinically significant
PCSK9	proprotein convertase subtilisin/kexin type 9
PPS	Per-Protocol Set
PT	preferred term
QD	once daily
QTcB	QT interval corrected for heart rate with Bazett's formula
QTcF	QT interval corrected for heart rate with Fridericia's formula
SAA	serum amyloid A
SAE	serious adverse event
SAS	Safety Analysis Set
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SOC	system organ class
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride
TSH	thyroid-stimulating hormone
ULN	upper limit of normal

VLDL-C	very low-density lipoprotein cholesterol
WHO	World Health Organization

4 INTRODUCTION

The purpose of this statistical analysis plan is to describe the framework for the reporting, summarization, and statistical analysis methodology of the safety and efficacy parameters measured throughout the study. It is based on Protocol GEM-301 (Amendment 3) dated 05 Oct 2016.

5 TRIAL OBJECTIVES

5.1 Primary Objectives

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

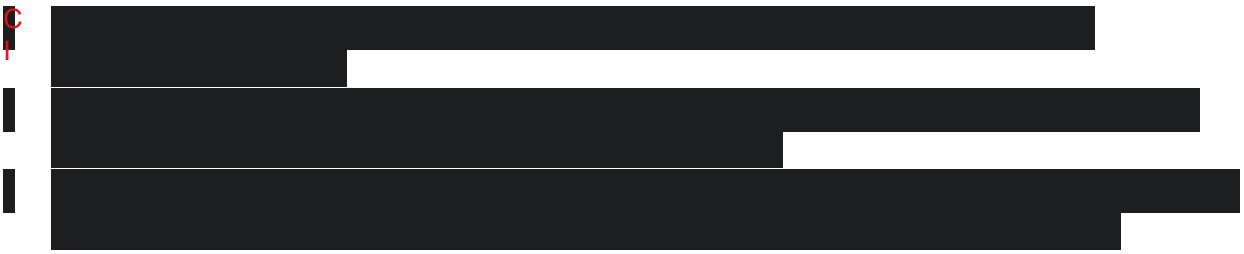
5.2 Secondary Objectives

The secondary objectives of this study are the following:

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

5.3 Exploratory Objectives

The exploratory objectives of this study are the following:



6 STUDY DESIGN CONSIDERATIONS

6.1 Study Design

This is a Phase 2, randomized, placebo-controlled, double-blind, multicenter study with a duration of up to 26 weeks with 12 weeks of study drug treatment. The study will consist of a Pre-Screening Visit (only for subjects requiring a wash-out period), a Screening Visit, a Treatment Period, and a Follow-up Visit.

Table 1. Overview of Study Periods

	Wash-out Period (for subjects requiring wash-out)	Screening Visit	Treatment Period
Study Days	Day -70 to -15, inclusive	Day -14 to -1, inclusive	Day 1 to 85, inclusive

Approximately 104 subjects will participate in the study at up to 20 sites in the United States. Subjects are required to be on either a high-intensity stable statin regimen (atorvastatin at 40 or 80 mg QD, or rosuvastatin at 20 or 40 mg QD) or a moderate-intensity stable statin regimen (atorvastatin at 10 or 20 mg QD, rosuvastatin at 5 or 10 mg QD, or simvastatin at 20 or 40 mg QD) with or without ezetimibe 10 mg QD for at least 12 weeks prior to the Screening Visit. Further, subjects must have a fasting LDL-C value ≥ 100 mg/dL (2.59 mmol/L) and a TG value < 500 mg/dL (5.65 mmol/L) at the Screening Visit, while on a stable, low-fat, low-cholesterol diet.

A wash-out period will be required for eligible subjects taking any lipid-regulating therapies or supplements except for atorvastatin at 10, 20, 40, or 80 mg QD, rosuvastatin at 5, 10, 20, or 40 mg QD, simvastatin at 20 or 40 mg QD, and/or ezetimibe at 10 mg QD. For subjects requiring a wash-out period, the Pre-Screening Visit will be their first study visit and will occur prior to the Screening Visit. The time between the Pre-Screening Visit and Screening Visit will depend on the required wash-out period duration which varies according to the status of a given subject's current lipid-regulating therapy. Specifically, PCSK9 inhibitors require an 8-week wash-out period, fibrates require a 6-week wash-out period, and niacins along with other lipid-regulating therapies including bile acid sequestrants require a 4-week wash-out period. For eligible subjects that do not require a wash-out period, the Screening Visit will be their first study visit.

Subjects will be randomized on Day 1 in a 1:1 ratio (gemcabene 600 mg to placebo). Randomization will be stratified by baseline statin-intensity regimen (moderate or high) and diabetes status (yes or no), both of which are recorded on the Medical History form at the subject's first visit (Pre-Screening or Screening Visit) and updated, when appropriate, at the Screening Visit. Subjects defined as diabetic are those receiving concomitant anti-diabetic medication at screening. Randomization within a baseline statin-intensity stratum will be capped at 52 subjects. By further stratifying on diabetes status at baseline, diabetic subjects will be evenly distributed across treatment groups within each statin-intensity stratum.

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

Study medication will be administered orally QD throughout the Treatment Period of the study. Subjects randomized to receive gemcabene 600 mg will take gemcabene 600 mg QD whereas subjects randomized to receive the placebo will take placebo QD. The first dose of the study drug will be administered at the site on Day 1. On all other days during the Treatment Period, the subject will self-dose.

6.2 Efficacy Measures

The primary efficacy measure is the percent change from baseline (CFBL) to Week 12 in fasting LDL-C (hereafter referred to as "LDL-C").

The secondary efficacy measures are:

- percent CFBL to Week 12 in LDL-C within each statin-intensity stratum (moderate, high);
- CFBL and percent CFBL to Weeks 2, 4, 8, and 12 in LDL-C;
- CFBL and percent CFBL to the average of Weeks 8 and 12 in LDL-C;
- CFBL and percent CFBL to Weeks 2, 4, 8, and 12 in non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), TG, HDL-C, and very low-density lipoprotein cholesterol (VLDL-C);
- percent of subjects achieving a LDL-C reduction from baseline of ≥ 10%, ≥ 15%, and ≥ 20% at Weeks 4, 8, and 12;
- percent of subjects achieving a LDL-C value < 100 mg/dL (2.59 mmol/L) at Weeks 4, 8, and 12;
- CFBL and percent CFBL to Weeks 4, 8 and 12 in ApoB , ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, ApoE, and lipoprotein(a) (Lp[a]);
- CFBL and percent CFBL to Week 12 in hsCRP, SAA, adiponectin, and fibrinogen; and
- CFBL to Week 12 in Framingham Risk Score (ie, 10-year risk of developing cardiovascular disease [CVD]).

The exploratory efficacy measures are:

[redacted]

- CI [redacted]

Developed using Framingham Heart Study data, [1, 2] the Framingham Risk Score is an estimate of a subject's 10-year risk of developing CVD which is computed using sex-specific algorithms that contain the following risk factors: age, systolic blood pressure (SBP), smoking status, TC, HDL-C, treatment for hypertension, and diabetes status. Smoking status refers to cigarette smoking status and will be collected once for each subject during the study and recorded on the Medical History CRF. Specifically, a smoker is defined as a subject where smoking is recorded on the Medical History CRF with a start date on or before first dose (ie, smoking start date ≤ day of first dose) and a stop date on or after first dose (ie, smoking stop date ≥ day of first dose). Partial and missing dates will be imputed using rules in Appendix 2. Appendix 3 contains anatomical therapeutic chemical (ATC) categories and descriptions that will be used to identify treatment for hypertension. A subject is considered to be receiving treatment for hypertension at baseline if there is at least 1 treatment for hypertension with a start date on or before first dose (ie, medication start date ≤ day of first dose) and a stop date on or after first dose (ie, medication stop date ≥ day of first dose). Partial and missing dates will be imputed using rules in Appendix 2. CVD comprises coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure. Please refer to Appendix 4 for the sex-specific algorithms that will be used to compute each subject's Framingham Risk Score at baseline and Week 12.

6.3 Safety Measures

Safety and tolerability measures include adverse events (AEs), safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis), 12-lead electrocardiograms (ECGs), physical examinations, vital signs, and weight. Regarding safety laboratory parameters, particular attention will be paid to hepatic (eg, alanine aminotransferase [ALT]/aspartate aminotransferase [AST], bilirubin, alkaline phosphatase [ALP]), renal (eg, blood urea nitrogen [BUN], serum creatinine, protein/creatinine ratio, albumin/creatinine ratio, neutrophil gelatinase-associated lipocalin [NGAL], urinalysis sediments, pH, electrolytes), and skeletal muscle (ie, creatine kinase) toxicities. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

7 STUDY POPULATIONS

7.1 Analysis Populations

A summary table containing the number of subjects in each of the populations defined below will be provided.

7.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all randomized subjects who receive at least 1 dose of the study drug and have at least 1 post-baseline efficacy assessment. Subjects will be classified according to the treatment they were randomized to. Efficacy analyses will be conducted using the FAS.

7.1.2 Per-Protocol Set

The Per-Protocol Set (PPS) includes all FAS subjects who complete the 12-week Treatment Period without major protocol deviations. Subjects will be classified according to the treatment they were randomized to. The PPS will be determined by the sponsor prior to treatment unblinding at the end of the study. The PPS will be used to assess the robustness of analysis results. Subjects excluded from the PPS and the reason for exclusion will be provided in the listings.

7.1.3 Safety Analysis Set

The Safety Analysis Set (SAS) consists of all randomized subjects who receive at least 1 dose of the study drug. Subjects will be classified according to the treatment they actually received. Safety analyses will be conducted using the SAS.

8 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

Although the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) Risk Category was specified in the protocol as a secondary endpoint, this was not computed because the CRFs did not collect all of the necessary information (family history of premature coronary heart disease).

Additionally, although the percent of diabetic subjects with > 5% decrease in dosage of anti-diabetes pharmacologic therapy from baseline to Week 12 was cited in the protocol as an exploratory endpoint, this analysis will not be conducted.

Although the protocol indicates that secondary analyses will be performed on subjects on and not on ezetimibe, these will not be done due to an insufficient number of subjects on ezetimibe.

Even though confirmatory analyses for secondary and exploratory analyses were detailed in the protocol, these will not be conducted.

Additionally, although percent CFBL to Weeks 2, 4, and 8 in LDL-C was not specified in the protocol, these analyses will be performed for completeness.

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 Sample Size Computation

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

9.2 General Conventions

In general, variables will be summarized using summary statistics. Frequency and percentages will be used for categorical variables whereas mean, SD, median, minimum, and maximum will be used to summarize continuous variables. Decimal precision for continuous variables will be based on the mean value; the median will contain the same number of decimal places as the mean, the SD will contain one more decimal place than the mean, and the minimum and maximum will contain one less decimal place than the mean. Typically, the mean will contain one more decimal place than actual values but decimal precision may vary in order to obtain an organized and understandable table or listing.

The first day of administration of randomized study medication (first dose) is defined as Study Day 1 or Day 1. All other study days will be computed relative to Day 1. For events on or after Day 1, study day for a particular event will be calculated as: $Date_{event} - Date_{first\ dose} + 1$. For events before Day 1, study day for a particular event will be calculated as: $Date_{event} - Date_{first\ dose}$. Day 0 will not be used.

All statistical testing will be 2-sided and performed at the alpha = 0.05 level. No multiplicity adjustments will be made for testing multiple secondary and exploratory efficacy outcomes. Given the large number of secondary and exploratory efficacy outcomes, p-values associated with such outcomes will be considered descriptive. As it is possible that some significant results could occur due to chance alone, undue consideration will not be given to isolated significant differences; rather, interpretation will be made based on patterns of significant differences and consistency with the primary outcome.

For a given parameter (eg, y) CFBL will be calculated as $y_t - y_b$, where y_t is a given subject's value *t* weeks post-baseline and y_b is a given subject's value at baseline. CFBL will be computed

for subjects with a baseline value and a post-baseline value. In order to be included in a CFBL analysis for a given parameter, a subject must have a baseline value. If a subject does not have a baseline value, they will be excluded from the CFBL analysis. If a subject is missing a post-baseline value, last observation carried forward (LOCF) will be used to impute the post-baseline value; only post-baseline values will be used for imputation. For example, if a value at Week 8 is missing and the corresponding Week 4 value is not missing, the Week 4 value will be carried forward. Considering that only post-baseline values can be used for imputation, it follows then that Week 2 summaries will only contain observed case data as there will be no post-baseline values to carry forward. Percent CFBL for a given subject and parameter will be computed as $\left(\frac{y_t - y_b}{y_b}\right) * 100$ (ie, CFBL divided by the baseline value and multiplied by 100). Percent CFBL will only be computed for subjects with a CFBL value. Additionally, subjects with a value of 0 at baseline will not have percent CFBL computed.

For efficacy parameters, end of treatment is defined as the last non-missing post-baseline value collected while on treatment or within 2 days of treatment (last dose) for a given subject. For safety parameters, end of treatment is defined as the last non-missing post-baseline value collected while on treatment or within 5 days of treatment (last dose).

The primary efficacy analysis will be conducted using analysis of covariance (ANCOVA). Secondary and exploratory analyses will utilize a similar approach except when the outcome of interest is binary; when the outcome of interest is binary, a logistic regression will be performed.

9.3 Baseline Definitions

Baseline for a given parameter is generally defined as the last assessment prior to the first dose of the study drug but varies depending on the parameter:

- Baseline for lipids (ie, LDL-C, non-HDL-C, TC, TG, HDL-C and VLDL-C) is defined as the average of the corresponding parameter's last 2 non-missing values between (and including) Screening and pre-dose Day 1. If only 1 value is available, it will be used for baseline.
- Baseline for apolipoproteins (ie, ApoB, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, ApoE, and Lp[a]), inflammatory biomarkers (ie, hsCRP, SAA, adiponectin and fibrinogen), serum Cl[redacted], fasting insulin, and FPG is defined as the corresponding parameter's last non-missing value between (and including) Screening and pre-dose Day 1.
- Baseline for HbA1c is defined as the value from the first visit (Pre-Screening or Screening Visit).
- Baseline for ECGs, vital signs, body mass index (BMI), weight, and safety laboratory parameters (ie, chemistry, hematology, coagulation, and urinalysis parameters) is defined as the last pre-dose measurement (pre-dose Study Day 1 or before) for the corresponding parameter.
- Baseline Framingham Risk Score for each subject will be computed using the following variables at the following time points: age at the Screening Visit, baseline TC (previously defined), baseline HDL-C, baseline SBP, treatment for hypertension at Day 1, smoking status at Day 1, and diabetes status at the Screening Visit.

9.4 Handling of Missing Data

Missing values at baseline will not be imputed in any situation. For efficacy analyses, values missing post-randomization will be imputed using LOCF (unless otherwise specified); only post-randomization values on treatment will be used for imputation. For example, if a subject has Week 12 efficacy parameters measured more than 2 days after their last dose, their Week 12 efficacy values will be imputed using the last non-missing value while on treatment (eg, Week 8). The imputed values will be used in summaries and analysis. For safety analyses, observed case data will be used.

Imputation will not be conducted for AEs missing severity or relationship to study medication. AEs missing severity will be excluded from summaries of AEs by severity. Adverse events missing relationship will be excluded from summaries of related AEs.

Rules for partial and missing dates for prior and concomitant medications and smoking status are given in Appendix 2.

Drug interruptions with partial start and/or stop dates will be assumed to be 1 day in length, and will be assumed to have occurred in the visit interval prior to when the interruption was collected (eg, if a drug interruption with partial dates was collected at the Week 8 visit, we will assume that the interruption occurred between the previous visit [eg, Week 4] and the Week 8 visit).

9.5 Interim Analysis

There is no planned interim analysis.

9.6 Visit Windows

Visit windows will be used to classify scheduled (except the Follow-up Visit), unscheduled, and early termination (ET) visits according to Table 2**.** below to ensure that all visits have the potential to contribute to summaries. If 2 or more visits occur within the same analysis window, data from the visit closest to the target day will be used in summaries and/or analysis; if the visits are the same distance from the target day, data from the later date will be used. Data for laboratory parameters scheduled to be measured post-randomization at only the Week 12 or ET Visit (ie, HbA1c, CI [redacted] hsCRP, SAA, fibrinogen, adiponectin, FPG, and insulin) will be summarized under the Week 12 Visit. If there is more than one value, the latest will be used. For efficacy, parameters measured after last dose + 2 days will not be considered. Except for adverse events, for safety, parameters measured after last dose + 5 days will not be considered.

Table 2. Visit Windows for Assessments Done at Day 1, Weeks 2, 4, 8, and 12[a]

Visit	Target Study Day	Visit Window
Day 1	1	(1)
Week 2	15	(2, 22)
Week 4	29	(23, 43)
Week 8	57	(44, 71)
Week 12	85	> 71

[a.] As Apo and select urinalysis parameters are not measured at Week 2, the Visit Window for Week 4 for Apo and urinalysis parameters is (2, 43). Remaining urinalysis parameters are not measured at Week 2 or Week 8; thus, the Visit Windows for Week 4 and Week 12 are (2, 57) and > 57, respectively.

10 STATISTICAL ANALYSIS METHODS

10.1 Subject Disposition

The number of subjects screened, reasons for screen failure, and the number of subjects randomized will be summarized for all screened subjects. Number of subjects who complete and discontinue the study, and reasons for study discontinuation that occur post-randomization will be summarized by randomized treatment group (ie, placebo and gemcabene 600 mg) for the FAS. Reasons for discontinuation will be categorized using the reasons provided on the CRF (ie, AE, prohibited medication, non-compliance, withdrawal by subject, lost to follow-up, death, termination by sponsor, and other reasons). Additionally, protocol deviations will be listed for all randomized subjects.

10.2 Demographics and Baseline Characteristics

Demographic information will be summarized using descriptive statistics by randomized treatment group and overall for the FAS. Additionally, demographic information will be presented by statin-intensity stratum (moderate and high), for diabetic subjects, and for subjects with and without mixed dyslipidemia. Explicitly, the following characteristics will be summarized:

- Sex (Male, Female);
- Menopausal Status for Females (post-menopausal or surgically sterile, pre-menopausal);
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown);
- Age;
- Height;
- Weight; and
- BMI,

where age will be computed for each subject using the following formula:

$$\text{Age} = \text{integer}([\text{Screening Visit date} - \text{date of birth}]/365.25),$$

and BMI will be calculated using the following formula:

$$\text{BMI} = (\text{body weight in kilograms})/(\text{height in meters})^2.$$

Pregnancy test results will be listed for female subjects.

Additionally, baseline primary and secondary endpoints along with 1 exploratory endpoint, CI [redacted] will be summarized for the FAS by randomized treatment group and overall. Specifically, the following parameters will be summarized at baseline: lipids, apolipoproteins, inflammatory biomarkers, and the Framingham Risk Score. This table will then be repeated for

each baseline statin-intensity stratum (moderate, high). Additionally, the number and percentage of diabetic subjects and subjects on and not on ezetimibe in each of the previously mentioned groups will be summarized for the FAS. A subject on ezetimibe is defined as a subject with ezetimibe recorded on the Concomitant Medications CRF with a start date on or before first dose (ie, medication start date ≤ day of first dose) and a stop date on or after first dose (ie, medication stop date ≥ day of first dose). Partial and missing dates will be imputed using rules in Appendix 2.

Further, for the subgroup of diabetic subjects within the FAS, baseline fasting insulin, FPG, HbA1c, lipids, apolipoproteins, and inflammatory biomarkers will be summarized by randomized treatment group and overall.

Lastly, for the subgroup of subjects with mixed dyslipidemia at baseline within the FAS, baseline lipids, apolipoproteins, and inflammatory biomarkers will be summarized by randomized treatment group and overall. This table will then be repeated for the subgroup of subjects without mixed dyslipidemia at baseline within the FAS.

For categorical parameters, denominators for percentages will be the number of subjects in the corresponding group (eg, gemcabene 600 mg) with non-missing data for the parameter of interest.

10.3 Treatment Compliance and Exposure

10.3.1 Treatment Compliance

Compliance with administration of study drug will be assessed at each study visit post-randomization during the Treatment Period and at the ET Visit, if applicable, and recorded on the appropriate CRF and the drug accountability log. Compliance will be computed using information collected on the Study Drug Interruption CRF. Specifically, compliance will be calculated for each subject at each scheduled post-randomization visit during the treatment period (and the ET visit, if applicable), where treatment period is defined as the time period bounded by the first dose date and last dose date, as (number of tablets taken since last visit/number of tablets that should have been taken since last visit)*100. As each subject is instructed to take 3 tablets per day during the treatment period, the number of tablets that should have been taken since the last visit will be computed as 3 tablets per day*number of days since last visit, where the number of days since the last visit will be computed as (day of visit - day of last visit + 1). Compliance will be summarized by visit and actual treatment group for the SAS.

For each subject, overall compliance will be computed as (number of tablets taken during treatment period/number of tablets that should have been taken during treatment period)*100. The number of tablets that should have been taken during the treatment period will be computed as 3 tablets per day* number of days during the treatment period, where the number of days during the treatment period will be computed as (last dose date – first dose date + 1). Subjects will then be grouped into categories of overall compliance (< 80%, 80% to 100%) according to their overall estimate of compliance. Overall compliance and categories of compliance will be summarized using descriptive statistics by actual treatment group for the SAS.

10.3.2 Treatment Exposure

Duration of exposure will be calculated for each subject as (last dose date – first dose date + 1) and will be summarized using descriptive statistics. The number of subjects who receive ≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 28 days, ≥ 42 days, ≥ 56 days, ≥ 70 days, and ≥ 84 days of the study medication will be presented by actual treatment group for the SAS.

Days on treatment will be computed as the number of days that the study medication was taken (ie, treatment exposure excluding days when the study medication was interrupted). Number of days on treatment and number of days study medication was interrupted for will be summarized for the SAS.

11 EFFICACY PARAMETERS

11.1 Primary Analysis

The primary efficacy endpoint (percent CFBL to Week 12 in LDL-C) will be analyzed using ANCOVA and the FAS population. The null hypothesis to be tested is that there is no difference in the expected percent CFBL to Week 12 in LDL-C between the active treatment (subjects treated with gemcabene 600 mg) and placebo (subjects treated with placebo) groups after adjusting for baseline statin-intensity stratum, baseline diabetes status, and baseline LDL-C. Explicitly, in the ANCOVA, percent CFBL to Week 12 in LDL-C will be the dependent variable whereas randomized treatment group (gemcabene 600 mg or placebo), baseline statin-intensity stratum (moderate or high), and baseline diabetes status (yes or no) will be included as factors, and baseline LDL-C will be included as a covariate. LOCF will be used to impute missing values for Week 12; only post-baseline values will be used for imputation. The least-squares mean (LSM) and standard error (SE) for percent CFBL to Week 12 in LDL-C for each treatment group and the least-squares mean and 95% confidence interval (CI) of the treatment difference will be produced from the model using type III sums of squares to estimate the magnitude of the treatment effect. The following SAS code will be used to conduct the ANCOVA:

```
proc glm data=data;
    class Drug(ref="Placebo") Diabetes StatinStrat;
    model pctCFBL = Drug Diabetes StatinStrat Base / solution;
    lsmeans Drug / stderr pdiff out=adjmeans;
run;
```

The following additional analyses will be performed to assess assumptions of ANCOVA. The assumptions of normality and homoscedasticity (equal variance) will be assessed using residuals from the ANCOVA. Explicitly, normality will be assessed by visually inspecting quantile-quantile plots and conducting the Shapiro-Wilk test. If normality is clearly violated, ranked ANCOVA will be conducted. Further, Levene's test will be conducted and residual plots will be visually assessed to determine if the assumption of homoscedasticity is met. Lastly, we will investigate the assumption of homogeneity of regression slopes across treatment groups (parallel slopes) by including the interaction between baseline LDL-C and treatment group in the model explicated previously. If results indicate that the interaction between baseline LDL-C and treatment group is not significant, we will assume that the assumption of parallel slopes is met. If the assumption of homoscedasticity or parallel slopes is clearly violated, the final model may be adjusted.

Confirmatory analysis will be conducted by performing the primary analysis using the PPS population.

11.2 Secondary Analysis

All secondary analyses will be conducted using the FAS population (or the specific subgroup within the FAS population, eg, diabetic subjects) with subjects included in their randomized treatment group regardless of the treatment they actually received.

Similar analysis of ANCOVA as specified for the primary analysis in the above section will be conducted for the secondary efficacy endpoints. Note that the covariate included in the ANCOVA will be the baseline value of the parameter of interest (eg, if the parameter of interest is HDL-C, the covariate in the ANCOVA will be HDL-C at baseline).

As previous research suggests that hsCRP and TG are non-normally distributed, [3, 4, 5], hsCRP and TG will be analyzed using ranked ANCOVA. [6] Results of parametric ANCOVA will also be provided for these parameters as supportive results. Ranked ANCOVA will be conducted by first ranking the outcome and covariate at a given timepoint (eg, Week 12) prior to conducting ANCOVA. The p-value corresponding to the difference in ranked outcome between treatment groups will be output, and results will be interpreted in the context of the median change from baseline for each treatment group. The SAS code for conducting ranked ANCOVA is provided below (this can be extended to percent change from baseline):

```
proc rank data=data out=data_rank ties=mean;
   var base chg;
   ranks r_base r_chg;
run;

proc glm data=data_rank;
   class Drug(ref="Placebo") Diabetes StatinStrat;
   model r_chg = Drug Diabetes StatinStrat r_base / solution;
   lsmeans Drug / stderr pdiff cl out=adjmeans;
quit;
```

The secondary efficacy endpoints that are binary will be analyzed using logistic regression. The output from each logistic regression model will include the odds ratio (OR), 95% CI, and the associated p-value. The SAS code for conducting a logistic regression model is provided below:

```
proc logistic data=data;
      class Drug(ref="Placebo") Diabetes StatinStrat;
      model Outcome(event="event")= Drug Diabetes StatinStrat Base / expb;
run;
```

The secondary efficacy analyses are:

- percent CFBL to Week 12 in LDL-C within each statin-intensity stratum (moderate, high);
- CFBL to Weeks 2, 4, 8, and 12 in LDL-C;
- percent CFBL to Weeks 2, 4, and 8 in LDL-C;
- CFBL and percent CFBL to the average of Weeks 8 and 12 in LDL-C;
- CFBL and percent CFBL to Weeks 2, 4, 8, and 12 in non-HDL-C, TC, TG, HDL-C, and VLDL-C;
- percent of subjects achieving a LDL-C reduction of ≥ 10%, ≥ 15%, and ≥ 20% at Weeks 4, 8, and 12 (separately);
- percent of subjects achieving a LDL-C value < 100 mg/dL (2.59 mmol/L) at Weeks 4, 8, and 12 (separately);

- CFBL and percent CFBL to Weeks 4, 8 and 12 in ApoB, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, ApoE, and Lp(a);
- CFBL and percent CFBL to Week 12 in hsCRP, SAA, adiponectin, and fibrinogen; and
- CFBL to Week 12 in Framingham Risk Score.

Percent CFBL to Week 12 in LDL-C within each statin-intensity stratum (moderate and high) will be analyzed using the same approach as the primary analysis except that baseline statin-intensity stratum will not be included in the model.

CFBL to Weeks 2, 4, 8, and 12 in LDL-C, percent CFBL to Weeks 2, 4, and 8 in LDL-C, and CFBL and percent CFBL to the average of Weeks 8 and 12 in LDL-C will be analyzed using the same approach as the primary analysis.

CFBL and percent CFBL to Weeks 2, 4, 8, and 12 in non-HDL-C, TC, TG, HDL-C, and VLDL-C, CFBL and percent CFBL to Weeks 4, 8 and 12 in ApoB, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, ApoE, and Lp(a), and CFBL and percent CFBL to Week 12 in hsCRP, SAA, adiponectin, and fibrinogen will be analyzed using the same approach as the primary analysis, except that hsCRP and TG will be analyzed with ranked ANCOVA.

Percent of subjects achieving an LDL-C reduction of ≥ 10%, ≥ 15%, and ≥ 20% at Weeks 4, 8, and 12 (compared to baseline), and percent of subjects achieving an LDL-C value < 100 mg/dL (2.59 mmol/L) at Weeks 4, 8, and 12 (compared to baseline) will be analyzed using logistic regression. Explicitly, we will estimate the odds of achieving the corresponding reduction (ie, ≥ 10%, ≥ 15%, and ≥ 20%) or an LDL-C value < 100 mg/dL at a given week using logistic regression. Randomized treatment group (gemcabene 600 mg or placebo), baseline statin-intensity stratum (moderate- or high-intensity), diabetes status (yes or no), and baseline LDL-C will be included in each model as factors.

Framingham Risk Score at baseline and Week 12 along with CFBL in Framingham Risk Score to Week 12 will be summarized by randomized treatment group using descriptive statistics. Framingham Risk Score at baseline has been explicated previously. Framingham Risk Score at Week 12 will be computed for each subject using the following variables at the following time points: age at the Screening Visit, TC at Week 12, HDL-C at Week 12, SBP at Week 12, treatment for hypertension at Week 12, smoking status at Day 1, and diabetes status at the Screening Visit. A subject is considered to be receiving treatment for hypertension at Week 12 if there is at least one treatment for hypertension with a start date on or before their Week 12 Visit (last dose) (ie, medication start date ≤ day of last dose) and a stop date on or after their Week 12 Visit (last dose) (ie, medication stop date ≥ day of last dose). Partial and missing dates will be imputed using rules in Appendix 2.

11.3 Exploratory Analysis

CI [redacted]

11.4 Manuscript Analysis

Please refer to Appendix 5. for additional analyses that will be performed for inclusion in a manuscript. Further, please note that results of these analyses will not be presented in the clinical study report.

12 SAFETY AND TOLERABILITY

Safety will be assessed through analysis of AEs, clinical laboratory assessments, ECGs, vital signs, and physical examinations for the SAS using descriptive statistics. Observed case data will be used. Additionally, summaries of safety data will be displayed by treatment group. Treatment group will be based on the treatment each subject actually received regardless of the treatment group they were randomized to. All safety data will be presented in listings.

12.1 Adverse Events

AEs will be coded using MedDRA version 19.1. Except for the AE overview table and summaries of serious adverse events (SAEs) and AEs resulting in death (both of which will include all AEs), AE tables will only include summaries of treatment-emergent adverse events (TEAEs). A TEAE is defined as an AE with a start date on or after the first dose date and less than 30 days after the last dose date. If the AE start date is missing, the AE is assumed to be a TEAE. An AE overview table containing the frequency and percent of the following will be summarized by treatment group, treatment group within each stratum, and treatment group within each statin type (atorvastatin, rosuvastatin, simvastatin):

- Number of subjects with at least one TEAE, drug-related TEAE, SAE, and drug-related SAE;
- Number of subjects who discontinued study treatment due to a TEAE, drug-related TEAE, SAE, and drug-related SAE;
- Number of subjects who had a study treatment interruption due to a TEAE;
- Number of subjects who discontinued the study due to a TEAE; and
- Number of deaths and deaths due to a drug-related TEAE.

Additionally, the following will be summarized by treatment group, and treatment group within each stratum:

- TEAEs by system organ class (SOC) and preferred term (PT);
- TEAEs by PT (decreasing frequency in the gemcabene group);
- TEAEs by SOC, PT, and maximum severity;
- Related TEAEs by SOC and PT;
- Related TEAEs by PT (decreasing frequency in the gemcabene group);
- SAEs by SOC and PT;
- Related SAEs by SOC and PT;
- Discontinuation of study treatment due to TEAEs by SOC and PT;
- Discontinuation of study treatment due to related TEAEs by SOC and PT; and
- AEs that resulted in death by SOC and PT.

Summaries of SOC and PT will be sorted alphabetically by SOC and by decreasing frequency of PT in the gemcabene group.

If a subject has more than 1 TEAE at a given level (eg, SOC and PT), the subject will only be counted once within that level. When summarizing TEAEs by maximum severity or causality, at each level of summarization, subjects who report 1 or more TEAEs within that level are only counted once at that level using the event of greatest severity (in severity tables) or strongest relationship to study drug (in causality tables). All tables will show the number and percent of subjects with at least 1 TEAE (or SAE, per the criteria on the table). For example, the table of related SAEs will include a row for number and percent of subjects with at least one related SAE. Additionally, a drug-related TEAE is defined as a TEAE with an assigned relationship of "related." A listing containing all AEs (pre-treatment and TEAEs) will be created; AEs that are not treatment-emergent will be flagged as non-treatment-emergent. Additionally, a listing containing AEs missing severity or relationship to the study drug will be provided; AEs that are not treatment-emergent will be flagged as non-treatment-emergent.

12.2 Clinical Laboratory Assessments

Standard clinical laboratory evaluations for safety chemistry, coagulation, and hematology will be conducted at all study visits and the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related AE). Clinically significant abnormal creatinine results at Week 12 (or the ET Visit, if applicable) will also be followed-up 2 weeks (± 3 days) after the last dose of study drug in addition to the 4 week (± 3 days) Follow-up Visit.

Additionally, a urine sample for urinalysis will be collected at the Pre-Screening Visit, if applicable, the Screening Visit, Day 1, Week 4, Week 8, Week 12, the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related AE), and the ET Visit, if applicable. A urine microscopic examination will be performed when the dipstick result is abnormal (positive for blood, leukocyte esterase, or nitrites). Urine protein/creatinine ratio and albumin/creatinine ratio will be performed at the Screening Visit, Day 1, Week 4, Week 12, the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related AE), and the ET Visit, if applicable. Urinary NGAL will be measured at Day 1, Week 4, Week 12, the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related AE), and the ET Visit, if applicable.

The following laboratory parameters will be summarized at baseline and at each post-baseline time point by treatment group. Additionally, CFBL to each time point (including end of treatment), if appropriate, for each of the following laboratory parameters will also be summarized by treatment group. If, for a given subject at a given visit, the absolute count of neutrophils are not provided but segmented and band neutrophils are, segmented and band neutrophils are summed to determine the absolute count of neutrophils. If only segmented neutrophils are provided, they are used as the absolute count of neutrophils. Similarly, if neutrophils/leukocytes are not provided at a given visit but neutrophils (segmented)/leukocytes are, neutrophils (segmented)/leukocytes are used as neutrophils/leukocytes. If a laboratory value is lower or higher than the detection limit, the value will not contribute to summary statistics but will be included in the listings.

- Chemistry: ALT, albumin, ALP, AST, bicarbonate, BUN, calcium, chloride, creatine kinase (CK), creatinine, gamma-glutamyl transferase (GGT), glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, (total) bilirubin, (total) protein, estimated glomerular filtration rate (GFR)
- Coagulation: prothrombin time, activated partial thromboplastin time, international normalized ratio
- Hematology: hemoglobin, hematocrit, leukocytes, basophils, eosinophils, lymphocytes, monocytes, neutrophils, platelets, red blood cell count, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular volume
- Urinalysis: pH, specific gravity, NGAL, creatinine, protein, protein/creatinine ratio, albumin, albumin/creatinine ratio

Out-of-range values will be assessed using shift tables. Laboratory values will be identified as low, normal, or high based on the normal ranges provided by the central laboratory. Shift tables for each parameter will display, for each treatment group, the number of subjects with low, normal, and high values at baseline and end of treatment. Additionally, a summary will be provided of the number of subjects who shifted to high or low during the study. The denominators will be the number of subjects at risk for shifting, ie, the subjects at risk for shifting to low are those with high or normal values at baseline, and the subjects at risk for shifting to high are those with low or normal values at baseline.

Potentially clinically significant (PCS) tables will also be used to summarize out-of-range values for safety laboratory parameters. The PCS values are found in Table 3. The number and percent of subjects meeting the criteria below for single occurrences and consecutive (multiple) occurrences will be summarized by treatment group. The number and percent of subjects meeting the criteria below for single occurrences will be repeated for each statin-intensity stratum. Summaries will be given for any time post-baseline. The denominator for a given percentage will be the number of subjects who had a post-baseline assessment for the corresponding parameter. Additionally, for subjects with at least 1 post-baseline laboratory value meeting the PCS criteria, all laboratory values will be provided in a listing.

Table 3. Lab PCS Criteria

Laboratory Parameter	Unit	PCS Criteria
ALT	U/L	> 2 × ULN
AST	U/L	> 2 × ULN
BUN	mg/dL	> 2 × ULN
Creatine kinase	U/L	> 3 × ULN
Creatinine	mg/dL	> 0.3 increase from baseline
Estimated GFR	mL/min	Decrease > 15 from baseline
Hemoglobin	g/dL	Decrease > 1.5 from baseline
Urinalysis Parameter	**Unit**	**PCS Criteria**
Blood	-	present
Protein (qualitative)	-	present
Protein (quantitative)	-	> ULN
Protein/creatinine ratio	mg/mmol	> ULN

Albumin/creatinine ratio	mg/mmol	> ULN

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, GFR = glomerular filtration rate, PCS = potentially clinically significant, ULN = upper limit of normal.

Urinalysis parameters that are not fully numeric (ie, blood, bilirubin, glucose, ketones, leukocyte esterase, protein [dipstick results], and nitrite) will be included in a listing.

Over the course of the study, there may be lab tests performed that were not specified in the protocol. These tests will not be summarized but will be included in the listings and flagged as non-protocol tests.

12.3 ECGs

ECGs will be performed in triplicate at the Screening Visit, Day 1, Week 2, Week 4, Week 8, Week 12, and the ET Visit, if applicable. The following ECG parameters will be reported by the central reader: heart rate, PR interval, QRS duration, QT interval (uncorrected), QT interval corrected for heart rate using Bazett's formula (QTcB) and using Fridericia's formula (QTcF), and T-wave amplitude. The average of the 3 values for a given ECG parameter (eg, heart rate) will be used for analysis. In cases where an ECG is performed in duplicate, the average will be used, and in cases where only one ECG is performed, the result of the single ECG will be used. CFBL and percent CFBL will be calculated for each parameter at each time point (including end of treatment) and summarized by treatment group.

Further, QTcB and QTcF will also be investigated through PCS tables (see Table 4 below for the criteria). The number and percent of subjects meeting the criteria below will be summarized by treatment group. Summaries will be given for both overall (ie, any time post-baseline) and by visit. Subjects will be included in all categories for which they qualify. For criteria on the "Actual" values, the denominator for the percentages is the number of subjects who had a post-baseline assessment for each parameter. For criteria on the change, the denominator is the number of subjects who had a baseline and post-baseline assessment.

Table 4. ECG PCS Criteria

ECG Parameter	Actual or Change	PCS Criteria
QTcB (msec)	Actual	> 450
	Actual	> 480
	Actual	> 500
	CFBL (increase)	> 30
	CFBL (increase)	> 60
QTcF (msec)	Actual	> 450
	Actual	> 480
	Actual	> 500
	CFBL (increase)	> 30
	CFBL (increase)	> 60

CFBL = change from baseline, ECG = electrocardiogram, PCS = potentially clinically significant, QTcB = QT interval corrected for heart rate with Bazett's formula, QTcF = QT interval corrected for heart rate with Fridericia's formula.

All interpretations along with the corresponding details will be provided in a listing.

12.4 Vital Signs and Weight

Vital signs comprise pulse rate, diastolic blood pressure (DBP), SBP, respiration rate, and temperature. Except for the Follow-up Visit, vital signs and weight will be measured at all study visits. CFBL and percent CFBL will be calculated for each vital sign and weight parameter at each time point (including end of treatment) and summarized by treatment group. Additionally, for DBP and SBP, the previous table will be presented by baseline hypertensive treatment status (yes or no) and treatment group.

Vital signs and weight will also be presented in a listing.

12.5 Physical Examinations

A full physical examination will be performed at each subject's first study visit (either at the Pre-Screening Visit or the Screening Visit) and last study visit (either at the Week 12 Visit or the ET Visit). At all other Study Visits (eg, Week 2) where a full physical examination was not conducted except the Follow-up Visit, a symptom-directed physical examination will be performed. Additionally, a symptom-directed physical examination will only be conducted at the Follow-up Visit for subjects who had an abnormal result at Week 12 (or the ET visit) or had an ongoing treatment-related AE.

For each assessment (general appearance, respiratory, etc.), the number and percentage of normal and abnormal findings will be provided by actual treatment group and visit for the SAS. The denominator used to calculate the percentage will be the number of subjects that underwent a physical examination at the corresponding visit.

13 OTHER RELEVANT DATA ANALYSES/SUMMARIES

13.1 Medical History

Medical history will be coded using MedDRA version 19.1. Medical history will be summarized by SOC and PT by actual treatment group for the SAS and will be presented in the listings. At each level of summarization, subjects who report one or more medical history events within a given level (SOC/PT) will only be counted once at that level. The table will be sorted by SOC (alphabetically) and then by PT (decreasing frequency in the gemcabene column within each SOC).

13.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version 01 Mar 2016. A prior medication is defined as a medication with a stop date prior to the date of the subject's first dose (ie, medication stop date < date of first dose). A concomitant medication is defined as a medication with a start date on or before the date of the subject's last dose (ie, medication start date ≤ date of last dose) and a stop date on or after the date of the subject's first dose (ie, medication stop date ≥ date of first dose); thus, a medication that is ongoing at the time of the subject's first dose is considered concomitant. Partial and missing dates will be imputed using rules in Appendix 2.

Prior and concomitant medications will be summarized in separate tables and listings. Medications will be summarized by ATC level 3 (level 3 indicates the therapeutic/pharmacologic subgroup) alphabetically and preferred name (decreasing frequency in the Gemcabene column within each ATC) by actual treatment group for the SAS. At each level of summarization, subjects who report one or more medications within a given level (eg, ATC and preferred name) will only be counted once at that level. Excluded medications will be flagged in the concomitant medications listing.

13.3 Concomitant Procedures

Concomitant procedures will be recorded on the concomitant medications CRF. A concomitant procedure is defined as a procedure with a start date on or before the date of the subject's last dose (ie, procedure start date ≤ date of last dose) and a stop date on or after the date of the subject's first dose (ie, procedure stop date ≥ date of first dose). Concomitant procedures will be presented in a listing containing verbatim terms for the SAS.

14 REFERENCES

1. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care the Framingham Heart Study. Circulation. 2008 Feb 12;117(6):743-53.

2. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998 May 1;97(18):1837-47.

3. Stein E, Bays H, Koren M, Bakker-Arkema R, Bisgaier C. Efficacy and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients. Journal of Clinical Lipidology. 2016 Oct 31;10(5):1212-22.

4. Meyer JM, Davis VG, McEvoy JP, Goff DC, Nasrallah HA, Davis SM, Daumit GL, Hsiao J, Swartz MS, Stroup TS, Lieberman JA. Impact of antipsychotic treatment on nonfasting triglycerides in the CATIE Schizophrenia Trial phase 1. Schizophrenia research. 2008 Aug 31;103(1):104-9.

5. Goldberg RB, Fonseca VA, Truitt KE, Jones MR. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. Archives of Internal Medicine. 2008 Jul 28;168(14):1531-40.

6. Conover WJ, Iman RL. Analysis of covariance using the rank transformation. Biometrics. 1982 Sep 1:715-24.

15 APPENDICES

Appendix 1. Schedule of Assessments and Procedures

		Screening [b]	Treatment Period [c]					Follow-up [d]	
	Pre-Screening [a]	up to Day-14	Day 1 [e]	Week 2 (Day 15 ± 3 days)	Week 4 (Day 29 ± 3 days)	Week 8 (Day 57 ± 3 days)	Week 12 (Day 85, or up to 3 days earlier)	Day 113 ± 3 days	
		Visit S1	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5		ET
Informed consent	X	X[f]							
Inclusion/exclusion criteria	X	X							
Medical/surgical history and demographics	X	X[f]							
Full physical examination[g]	X	X[f]					X		X
Symptom-directed physical examination		X[h]	X	X	X	X		X[i]	
Vital signs[j], height[k], and weight	X	X	X	X	X	X	X		X
Body Mass Index (BMI)	X	X							
Urinalysis[l]	X	X	X		X	X	X	X[i]	X
Serum/urine pregnancy test[m]	X	X	X	X	X	X	X		X
Safety chemistry panel, coagulation, and hematology[n]	X	X	X	X	X	X	X	X[i]	X
TSH, HbA1c, and serology[o]	X	X[f]					X		X
Fasting lipid panel[p]; LDL-C ultracentrifugation when necessary	X[q]	X	X	X	X	X	X		X
Fasting apolipoproteins[r]			X		X	X	X		X
PCSK9			X				X		X
hsCRP, SAA, fibrinogen, and adiponectin			X				X		X
Fasting plasma glucose, insulin			X				X		X
Randomization			X						
Study drug administration[s]			X	X	X	X	X		
Dispense study drug and instructions			X	X	X	X			

	Pre-Screening [a]	Screening [b] up to Day-14	Day 1 [e]	Week 2 (Day 15 ± 3 days)	Week 4 (Day 29 ± 3 days)	Week 8 (Day 57 ± 3 days)	Week 12 (Day 85, or up to 3 days earlier)	Follow-up [d] Day 113 ± 3 days	
		Treatment Period [c]							
	Visit S1	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5		ET
Compliance check				X	X	X	X		X
Dietary instructions[t]	X	X	X	X	X	X			
12-lead ECG[u]		X	X	X	X	X	X		X
Initiate wash-out	X								
Adverse events	X[v]	X[v]	X	X	X	X	X	X	X
Concomitant medications	X	X[f]	X	X	X	X	X	X	X
Reserve samples			X	X	X	X	X		X

Apo = apolipoprotein, BMI = body mass index, ECG = electrocardiogram, eCRF = electronic case report form, ET = Early Termination, HBV = hepatitis B virus, HbA1c = hemoglobin A1c, HCV = hepatitis C virus, HDL-C = high-density lipoprotein cholesterol, HIV = human immunodeficiency virus, HoFH = homozygous familial hypercholesterolemia, hsCRP = high sensitivity C-reactive protein, LDL-C = low density lipoprotein cholesterol, Lp(a) = lipoprotein(a), NCEP ATP-III = National Cholesterol Education Program Adult Treatment Panel III, NGAL = neutrophil gelatinase-associated lipocalin, non-HDL-C = non-high-density lipoprotein cholesterol, CI [redacted] CI [redacted] SAA = serum amyloid A, TC = total cholesterol, TG = triglyceride, TSH = thyroid-stimulating hormone, VLDL-C = very low density lipoprotein cholesterol.

[a] Only subjects requiring a wash-out period will participate in the Pre-Screening Visit. Specifically, CI [redacted] inhibitors will require an 8-week wash-out period, fibrates will require a 6-week wash-out period, and niacins or other lipid-regulating therapies such as bile acid sequestrants will require a 4-week wash-out period, prior to the Screening Visit.

[b] All eligible subjects will participate in the Screening Visit up to 14 days prior to Day 1. For subjects taking the required stable statin therapy for > 4 weeks at the Screening Visit and do not require a wash-out period, the Screening Visit will be their first study visit.

[c] Study assessments will be completed ± 3 days of given time point for all study visits from Day 1 through Week 8. Week 12 assessments can be performed up to 3 days prior to Week 12, but not after Week 12.

[d] The Follow-up Visit will be conducted as a telephone call 4 weeks (± 3 days) after the last dose of study drug, unless the subject requires a site visit due to an abnormal result at Week 12 (or the ET Visit, if applicable) or an ongoing treatment-related adverse event.

[e] Procedures will be performed pre-dose. The Investigator will inquire with the subject at Day 1 to determine if there have been any changes in the subject's health affecting eligibility or requiring an update to their medical and surgical history.

[f] For subjects who required a wash-out period and completed the Pre-Screening Visit, the following Screening Visit procedures will not be repeated: informed consent, full physical examination, height, TSH, HbA1c, and serology (HBV, HCV, and HIV) screening. Updates, as needed, will be made to medical/surgical history, demographics, and concomitant medications.

[g] A full physical examination includes genitourinary examination per the Investigator's discretion and does not include a rectal examination.

[h] Only for subjects who required a wash-out period and completed the full physical examination at the Pre-Screening Visit.

[i] Only for subjects who had an abnormal result at Week 12 (or the ET Visit, if applicable) or an ongoing treatment-related adverse event.

[j] Vital signs include pulse rate, blood pressure, respiration rate, and temperature. Blood pressure should be obtained in the seated position, after the subject has rested comfortably for at least 5 minutes. Blood pressure at the Screening Visit should be obtained in both arms and the arm with the highest value should be used for ongoing

	Pre-Screening [a]	Screening [b] up to Day-14	Treatment Period [c] Day 1 [e]	Week 2 (Day 15 ± 3 days)	Week 4 (Day 29 ± 3 days)	Week 8 (Day 57 ± 3 days)	Week 12 (Day 85, or up to 3 days earlier)	Follow-up [d] Day 113 ± 3 days	
	Visit S1	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5		ET

monitoring throughout the rest of the study. If an automated assessment is performed, the same machine should be used for the subject throughout the study when possible. Care should be taken to ensure an appropriate cuff size is utilized.

k Height will be measured only at the subject's first study visit, either at the Pre-Screening Visit or the Screening Visit.

l A urine microscopic examination will be performed when the dipstick result is abnormal (positive for blood, leukocyte esterase, or nitrites). Urine protein:creatinine ratio (albumin:creatinine) will be performed at the Screening Visit, Day 1, Week 4, Week 12, the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event), and the ET Visit, if applicable. Urinary NGAL will be measured at Day 1, Week 4, Week 12, the Follow-up Visit (only for subjects who had an abnormal result at Week 12 [or the ET Visit, if applicable] or an ongoing treatment-related adverse event), and the ET Visit, if applicable.

m For women of child-bearing potential only, a serum pregnancy test will be conducted at the Screening Visit, Week 12, and the ET Visit, if applicable. A urine pregnancy test will be conducted at the Pre-Screening Visit, Day 1, Week 2, Week 4, and Week 8.

n Clinically significant abnormal creatinine results at Week 12 (or the ET Visit, if applicable) will also be followed-up 2 weeks (± 3 days) after the last dose of study drug in addition to the Week 4 (± 3 days) Follow-up Visit. See Appendix B in the protocol for a list of analytes and description of when repeat or reflexive testing will be required.

o Thyroid-stimulating hormone, HbA1c, and serology (HBV, HCV, and HIV) will be measured at the subject's first study visit, either at the Pre-Screening Visit, if applicable, or the Screening Visit. Only HbA1c will be measured at Week 12, and the ET Visit, if applicable.

p Includes LDL-C, non-HDL-C, TC, TG, HDL-C, and VLDL-C. Fasting will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Subjects will be permitted to have water.

q Includes LDL-C and TG only. Fasting will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Subjects will be permitted to have water.

r Includes ApoB, ApoA-I, ApoA-II, ApoA-V, ApoC-II, ApoC-III, ApoE, and Lp(a). Fasting will be defined as no food or caloric beverage for at least 10 hours prior to sample collection. Subjects will be permitted to have water.

s Study drug will be administered at the site on Day 1. Subjects will self-dose at all other times during the Treatment Period.

t Subjects will be counseled on a low-fat, low-cholesterol diet (NCEP ATP-III guidelines or equivalent).

u Subjects should be lying quietly in a fully supine position for at least 10 minutes prior to each 12-lead ECG.

v Serious adverse events that occur prior to the first dose of study drug (Day 1) should be reported as an update to medical history as well as be reported on the appropriate adverse event eCRF.

Appendix 2. Prior and Concomitant Medications and Smoking Status Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
Start date	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date of first dose of study drug
Stop date	D only	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Last day of month
	M and D	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
	M, D, and Y	None - date completely missing and NOT ongoing	Date of last dose of study drug

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 3. ATC Categories and Descriptions of Hypertensive Treatments

The WHO Drug Dictionary version 01 Mar 2016 was used to identify the following ATC categories and descriptions which will be used to identify hypertensive treatment.

ATC2/ATC2 Description[1]	ATC3/ATC3 Description	ATC4/ATC4 Description
C02/ANTIHYPERTENSIVES	C02A/ ANTIADRENERGIC AGENTS, CENTRALLY ACTING	C02AA/ Rauwolfia alkaloids
C02/ANTIHYPERTENSIVES	C02A/ ANTIADRENERGIC AGENTS, CENTRALLY ACTING	C02AB/Methyldopa
C02/ANTIHYPERTENSIVES	C02A/ ANTIADRENERGIC AGENTS, CENTRALLY ACTING	C02AC/Imidazoline receptor agonists
C02/ANTIHYPERTENSIVES	C02B/ANTIADRENERGIC AGENTS, GANGLION-BLOCKING	C02BA/Sulfonium derivatives
C02/ANTIHYPERTENSIVES	C02B/ANTIADRENERGIC AGENTS, GANGLION-BLOCKING	C02BB/Secondary and tertiary amines
C02/ANTIHYPERTENSIVES	C02B/ANTIADRENERGIC AGENTS, GANGLION-BLOCKING	C02BC/Bisquaternary ammonium compounds
C02/ANTIHYPERTENSIVES	C02C/ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING	C02CA/Alpha-adrenoreceptor antagonists
C02/ANTIHYPERTENSIVES	C02C/ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING	C02CC/Guanidine derivatives
C02/ANTIHYPERTENSIVES	C02D/ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON	C02DA/Thiazide derivatives
C02/ANTIHYPERTENSIVES	C02D/ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON	C02DB/Hydrazinophthalazine derivatives
C02/ANTIHYPERTENSIVES	C02D/ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON	C02DC/Pyrimidine derivatives
C02/ANTIHYPERTENSIVES	C02D/ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON	C02DD/Nitroferricyanide derivatives
C02/ANTIHYPERTENSIVES	C02D/ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON	C02DG/Guanidine derivatives
C02/ANTIHYPERTENSIVES	C02K/OTHER ANTIHYPERTENSIVES	C02KA/Alkaloids, excl. rauwolfia
C02/ANTIHYPERTENSIVES	C02K/OTHER ANTIHYPERTENSIVES	C02KB/Tyrosine hydroxylase inhibitors
C02/ANTIHYPERTENSIVES	C02K/OTHER ANTIHYPERTENSIVES	C02KC/MAO inhibitors
C02/ANTIHYPERTENSIVES	C02K/OTHER ANTIHYPERTENSIVES	C02KD/Serotonin antagonists
C02/ANTIHYPERTENSIVES	C02K/OTHER ANTIHYPERTENSIVES	C02KW/Herbal antihypertensives, other
C02/ANTIHYPERTENSIVES	C02K/OTHER ANTIHYPERTENSIVES	C02KX/Antihypertensives for pulmonary arterial hypertension
C02/ANTIHYPERTENSIVES	C02L/ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LA/Rauwolfia alkaloids and diuretics in combination
C02/ANTIHYPERTENSIVES	C02L/ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LB/Methyldopa and diuretics in combination
C02/ANTIHYPERTENSIVES	C02L/ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LC/Imidazoline receptor agonists in combination with diuretics

C02/ANTIHYPERTENSIVES	C02L/ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LE/Alpha-adrenoreceptor antagonists and diuretics
C02/ANTIHYPERTENSIVES	C02L/ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LF/Guanidine derivatives and diuretics
C02/ANTIHYPERTENSIVES	C02L/ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LG/Hydrazinophthalazine derivatives and diuretics
C02/ANTIHYPERTENSIVES	C02L/ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LK/Alkaloids, excl. rauwolfia, in combination with diuretics
C02/ANTIHYPERTENSIVES	C02L/ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LL/MAO inhibitors and diuretics
C02/ANTIHYPERTENSIVES	C02L/ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LN/Serotonin antagonists and diuretics
C02/ANTIHYPERTENSIVES	C02L/ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	C02LX/Other antihypertensives and diuretics
C02/ANTIHYPERTENSIVES	C02N/COMBINATIONS OF ANTIHYPERTENSIVES IN ATC-GR. C02	-
C03/DIURETICS	C03A/LOW-CEILING DIURETICS, THIAZIDES	C03AA/Thiazides, plain
C03/DIURETICS	C03A/LOW-CEILING DIURETICS, THIAZIDES	C03AB/Thiazides and potassium in combination
C03/DIURETICS	C03A/LOW-CEILING DIURETICS, THIAZIDES	C03AH/Thiazides, combinations with psycholeptics and/or analgesics
C03/DIURETICS	C03A/LOW-CEILING DIURETICS, THIAZIDES	C03AX/Thiazides, combinations with other drugs
C03/DIURETICS	C03B/LOW-CEILING DIURETICS, EXCL. THIAZIDES	C03BA/Sulfonamides, plain
C03/DIURETICS	C03B/LOW-CEILING DIURETICS, EXCL. THIAZIDES	C03BB/Sulfonamides and potassium in combination
C03/DIURETICS	C03B/LOW-CEILING DIURETICS, EXCL. THIAZIDES	C03BC/Mercurial diuretics
C03/DIURETICS	C03B/LOW-CEILING DIURETICS, EXCL. THIAZIDES	C03BD/Xanthine derivatives
C03/DIURETICS	C03B/LOW-CEILING DIURETICS, EXCL. THIAZIDES	C03BK/Sulfonamides, combinations with other drugs
C03/DIURETICS	C03B/LOW-CEILING DIURETICS, EXCL. THIAZIDES	C03BX/Other low-ceiling diuretics
C03/DIURETICS	C03C/HIGH-CEILING DIURETICS	C03CA/Sulfonamides, plain
C03/DIURETICS	C03C/HIGH-CEILING DIURETICS	C03CB/Sulfonamides and potassium in combination
C03/DIURETICS	C03C/HIGH-CEILING DIURETICS	C03CC/Aryloxyacetic acid derivatives
C03/DIURETICS	C03C/HIGH-CEILING DIURETICS	C03CD/Pyrazolone derivatives
C03/DIURETICS	C03C/HIGH-CEILING DIURETICS	C03CX/Other high-ceiling diuretics
C03/DIURETICS	C03D/POTASSIUM-SPARING AGENTS	C03DA/Aldosterone antagonists
C03/DIURETICS	C03D/POTASSIUM-SPARING AGENTS	C03DB/Other potassium-sparing agents

C03/DIURETICS	C03E/DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION	C03EA/Low-ceiling diuretics and potassium-sparing agents
C03/DIURETICS	C03E/DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION	C03EB/High-ceiling diuretics and potassium-sparing agents
C03/DIURETICS	C03X/OTHER DIURETICS	C03XA/Vasopressin antagonists
C03/DIURETICS	C03X/OTHER DIURETICS	C03XW/Herbal diuretics, other
C07/BETA BLOCKING AGENTS	C07A/BETA BLOCKING AGENTS	C07AA/Beta blocking agents, non-selective
C07/BETA BLOCKING AGENTS	C07A/BETA BLOCKING AGENTS	C07AB/Beta blocking agents, selective
C07/BETA BLOCKING AGENTS	C07A/BETA BLOCKING AGENTS	C07AG/Alpha and beta blocking agents
C07/BETA BLOCKING AGENTS	C07B/BETA BLOCKING AGENTS AND THIAZIDES	C07BA/Beta blocking agents, non-selective, and thiazides
C07/BETA BLOCKING AGENTS	C07B/BETA BLOCKING AGENTS AND THIAZIDES	C07BB/Beta blocking agents, selective, and thiazides
C07/BETA BLOCKING AGENTS	C07B/BETA BLOCKING AGENTS AND THIAZIDES	C07BG/Alpha and beta blocking agents and thiazides
C07/BETA BLOCKING AGENTS	C07C/BETA BLOCKING AGENTS AND OTHER DIURETICS	C07CA/Beta blocking agents, non-selective, and other diuretics
C07/BETA BLOCKING AGENTS	C07C/BETA BLOCKING AGENTS AND OTHER DIURETICS	C07CB/Beta blocking agents, selective, and other diuretics
C07/BETA BLOCKING AGENTS	C07C/BETA BLOCKING AGENTS AND OTHER DIURETICS	C07CG/Alpha and beta blocking agents and other diuretics
C07/BETA BLOCKING AGENTS	C07D/BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS	C07DA/Beta blocking agents, non-selective, thiazides and other diuretics
C07/BETA BLOCKING AGENTS	C07D/BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS	C07DB/Beta blocking agents, selective, thiazides and other diuretics
C07/BETA BLOCKING AGENTS	C07E/BETA BLOCKING AGENTS AND VASODILATORS	C07EA/Beta blocking agents, non-selective, and vasodilators
C07/BETA BLOCKING AGENTS	C07E/BETA BLOCKING AGENTS AND VASODILATORS	C07EB/Beta blocking agents, selective, and vasodilators
C07/BETA BLOCKING AGENTS	C07F/BETA BLOCKING AGENTS AND OTHER ANTIHYPERTENSIVES	C07FA/Beta blocking agents, non-selective, and other antihypertensives
C07/BETA BLOCKING AGENTS	C07F/BETA BLOCKING AGENTS AND OTHER ANTIHYPERTENSIVES	C07FB/Beta blocking agents, selective, and other antihypertensives
C08/CALCIUM CHANNEL BLOCKERS	C08C/SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	C08CA/Dihydropyridine derivatives
C08/CALCIUM CHANNEL BLOCKERS	C08C/SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	C08CX/Other selective calcium channel blockers with mainly vascular effects
C08/CALCIUM CHANNEL BLOCKERS	C08D/SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS	C08DA/Phenylalkylamine derivatives

C08/CALCIUM CHANNEL BLOCKERS	C08D/SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS	C08DB/Benzothiazepine derivatives
C08/CALCIUM CHANNEL BLOCKERS	C08E/NON-SELECTIVE CALCIUM CHANNEL BLOCKERS	C08EA/Phenylalkylamine derivatives
C08/CALCIUM CHANNEL BLOCKERS	C08E/NON-SELECTIVE CALCIUM CHANNEL BLOCKERS	C08EX/Other non-selective calcium channel blockers
C08/CALCIUM CHANNEL BLOCKERS	C08G/CALCIUM CHANNEL BLOCKERS AND DIURETICS	C08GA/Calcium channel blockers and diuretics
C09/AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09A/ACE INHIBITORS, PLAIN	C09AA/ACE inhibitors, plain
C09/AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09B/ACE INHIBITORS, COMBINATIONS	C09BA/ACE inhibitors and diuretics
C09/AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09B/ACE INHIBITORS, COMBINATIONS	C09BB/ACE inhibitors and calcium channel blockers
C09/AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09B/ACE INHIBITORS, COMBINATIONS	C09BX/ACE inhibitors, other combinations
C09/AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09C/ANGIOTENSIN II ANTAGONISTS, PLAIN	C09CA/Angiotensin II antagonists, plain
C09/AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09D/ANGIOTENSIN II ANTAGONISTS, COMBINATIONS	C09DA/Angiotensin II antagonists and diuretics
C09/AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09D/ANGIOTENSIN II ANTAGONISTS, COMBINATIONS	C09DB/Angiotensin II antagonists and calcium channel blockers
C09/AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09D/ANGIOTENSIN II ANTAGONISTS, COMBINATIONS	C09DX/Angiotensin II antagonists, other combinations
C09/AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09X/OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09XA/Renin-inhibitors

ATC = anatomical therapeutic chemical, MAO = monoamine oxidase, ACE = angiotensin-converting enzyme

[1] All medications listed have ATC1/ATC1 Description=C/CARDIOVASCULAR SYSTEM.

Appendix 4. Sex-specific Framingham Risk Score algorithms

Framingham Risk Score (10-year CVD risk) for each subject is based on sex-specific Cox proportional hazard models. [1] Explicitly, the algorithm to compute Framingham Risk Score for each subject is:

$$\hat{p} = 1 - S_0(t)^{\exp(\sum_{i=1}^{p} \beta_i X_i - \sum_{i=1}^{p} \beta_i \bar{X}_i)},$$

where $S_0(t)$ is baseline survival at follow-up time t (10 years), β_i is the estimated regression coefficient (log hazard ratio), X_i is the log-transformed value of the i-th risk factor if continuous, $\bar{X}_i$ is the corresponding mean, and p denotes the number of risk factors. For women, baseline 10-year survival is 0.95012. For men, the baseline 10-year survival is 0.88936.

Appendix 5. Manuscript Analyses

The following additional analyses will be performed for possible inclusion in a manuscript using the FAS. These results will not be included in the CSR. For analyses within a given baseline statin-intensity stratum, baseline statin-intensity stratum will not be included in the model (where appropriate).

- In addition to percent CFBL to Week 12 in LDL-C, all other secondary efficacy analyses will be conducted within each baseline statin-intensity stratum.