Title: A 12-Week, Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy Safety and Tolerability of Gemcabene in Subjects with Severe Hypertriglyceridemia (INDIGO-1)

NCT ID: NCT02944383

Approval Date: 02-May-2018

16.1.9 DOCUMENTATION OF STATISTICAL METHODS

Statistical Analysis Plan: GEM-401

Statistical Analysis Plan: GEM-401

Study Title:	A 12-Week, Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy Safety and Tolerability of Gemcabene in Subjects with Severe Hypertriglyceridemia (INDIGO-1)
Study Number:	GEM-401
Study Phase:	Phase 2
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Confidentiality Statement

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Study Title: A 12-Week, Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy Safety and Tolerability of Gemcabene in Subjects with Severe Hypertriglyceridemia (INDIGO-1)

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANGPTL4	angiopoietin like 4
Apo	apolipoprotein
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
BUN	blood urea nitrogen
CFBL	change from baseline
CRF	case report form
DPP	dipeptidyl peptidase
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
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
IL-6	interleukin-6
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
LDL-TG	low-density lipoprotein triglyceride
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
NCEP ATP-III	National Cholesterol Education Program Adult Treatment Panel III
NGAL	neutrophil gelatinase-associated lipocalin
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
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 CHANGES IN CONDUCT AND PLANNED ANALYSES FROM THE PROTOCOL

4.1 Unblinding After Last Patient Last Visit at Week 12

The protocol states that the blind is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of subject safety. However, when the final subject has completed the double-blind portion of the study (ie., the Week 12 visit), the process of unblinding will begin.

Once the last patient has completed the Week 12 visit, an unblinded team (separate from the study team) consisting of at least one unblinded statistician and one unblinded programmer will request the treatment codes, perform unblinding activities, and provide a subset of summary results to Gemphire. All data for subjects completed through Week 12 will be cleaned and frozen to facilitate delivery of the Week 12 results, and no results beyond Week 12 will be provided in this delivery. The final database lock will occur after the 4-week follow-up for all subjects as planned, and the remaining outputs will be delivered following database lock.

The study team will not be unblinded to individual subjects and will only be unblinded to select overall results at the treatment group level. Additional details regarding the specifics of who will be unblinded and when will be included in a separate memo, which will be finalized prior to the Week 12 unblinding.

4.2 Clarifications to Schedule of Procedures

The schedule of procedures table in the protocol indicates that fasting lipid panel will be assessed at every study visit including the follow-up visit. However, fasting lipid panel will not be assessed at the follow-up visit.

4.3 Clarifications and Changes in Analyses

The following list provides changes from the protocol reflected in the SAP:

- The protocol states that a parametric analysis of covariance (ANCOVA) will be completed for primary, secondary and exploratory endpoints; and that either the data would be transformed (and analyzed using ANCOVA) or that a non-parametric test would be used if the assumption of normality is violated. However for consistency with prior studies in hypertriglyceridemia, an ANCOVA on the ranked-transformed data will be considered the main analysis for these endpoints.

- 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, as it was determined that this analysis would be inconclusive due to the way patients were recruited.

- Confirmatory analyses (using the per protocol set) for secondary and exploratory analyses were detailed in the protocol, but these will not be conducted.

- Sampling for ApoA-V was delayed and will be eliminated. Therefore, secondary and exploratory analyses for ApoA-V will not be performed.

- The protocol indicates that treatment, baseline statin stratum (yes or no), and baseline (covariate) will be included in the secondary and exploratory ANCOVA models as factors. However, as the qualifying TG stratum (> 880 mg/dL and ≤ 880 mg/dL) was a stratification factor for this study, it will also be included as a factor in all secondary and exploratory ANCOVA models for all parameters except Triglycerides (TGs).

5 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-401 Version 4.0 dated 17 Mar 2017.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Objectives

6.1.1 Primary Objective

The primary objective of this study is to assess the effect of gemcabene 300 mg and 600 mg once daily (QD) compared to placebo on fasting serum TG levels after 12 weeks of treatment in subjects with severe hypertriglyceridemia (≥ 500 mg/dL to < 1500 mg/dL) on a self-reported, stable, heart-healthy diet.

6.1.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess the safety and tolerability of gemcabene 300 mg and 600 mg QD in subjects with severe hypertriglyceridemia;
- To assess the effect of gemcabene 300 mg and 600 mg QD on other lipid and apolipoprotein parameters, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), serum amyloid A (SAA), angiopoietin like 4 (ANGPTL4), adiponectin, and fibrinogen after 12 weeks of treatment.

6.1.3 Exploratory Objectives

The exploratory objectives are the following:

- CI [redacted]

- CI [redacted]

6.2 Endpoints

6.2.1 Primary Endpoint

The primary efficacy endpoint is the percent change in fasting serum TG from baseline to end of study (EOS).

6.2.2 Secondary Endpoints

The secondary endpoints are as follows:

- Change and percent change from baseline to Weeks 2, 6, 10, and 12 in fasting serum TG, and change from baseline to EOS in fasting serum TG;
- Change and percent change from baseline to Weeks 2, 6, 10, 12, and EOS in total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), HDL-C, and very low-density lipoprotein cholesterol (VLDL-C);
- Change and percent change from baseline to Weeks 10, 12, and EOS in apolipoprotein (Apo) B, ApoA-I, ApoA-II, ApoC-II, ApoC-III, and ApoE;
- Change and percent change from baseline to Weeks 10, 12, and EOS in low-density lipoprotein cholesterol (LDL-C) (ultracentrifugation), low-density lipoprotein triglyceride (LDL-TG), VLDL-TG, HDL-TG;
- Change and percent change from baseline to Week 12 in lipoprotein size and particle number (NMR);
- Change and percent change from baseline to Weeks 10, 12, and EOS in hsCRP, IL-6, SAA, adiponectin, and fibrinogen; and
- Percent of subjects achieving a TG value < 500 mg/dL (5.65 mmol/L) at Weeks 10, 12, and EOS.
- Secondary endpoints related to safety include adverse events (AEs), safety laboratory parameters (chemistry including cystatin-C, hematology, coagulation values); urinalysis including urine protein:creatinine ratio, urine albumin:creatinine ratio and neutrophil gelatinase-associated lipocalin (NGAL); vital signs, electrocardiogram (ECG) results; and physical examinations (PEs).

6.2.3 Exploratory Endpoints

The exploratory efficacy endpoints are as follows:

- CI [redacted]

- CI [redacted]

[redacted]

Appendix 3 contains anatomical therapeutic chemical (ATC) categories and descriptions that will be used to identify anti-diabetes pharmacologic therapy for subjects. If an anti-diabetes pharmacologic therapy has a start date on or before first dose of study drug (ie, medication start date less than, or equal to day of first dose of study drug) and a stop date on or after first dose of study drug (ie, medication stop date greater than, or equal to day of first dose of study drug) it will be used in analysis. Partial and missing dates will be imputed using rules in Appendix 2.

7 STUDY DESIGN CONSIDERATIONS

7.1 Study Design

This is a Phase 2, randomized, double-blind, parallel-group, multi-center study. Total study duration will be 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), up to 3 Screening Visits, a 12-week Treatment Period (with 5 Visits), and a Follow-up Visit (4 weeks after the last dose).

Table 1. Overview of Study Periods

	Wash-out Period (for subjects requiring wash-out)	Screening Visit	Treatment Period
Study Days	Day -84 to -29, inclusive	Day -28 to -1, inclusive	Day 1 to 85, inclusive

Approximately 90 subjects with severe hypertriglyceridemia (TG ≥ 500 mg/dL to < 1500 mg/dL) will participate in the study from approximately 40-50 sites in the United States and Canada.

Pre-Screening (Wash-Out Period): A wash-out period will be required for potential subjects taking any lipid-regulating therapies or supplements, with the exception of statins or ezetimibe 10 mg QD. Subjects may initiate the wash-out period, if meeting all other criteria and have a qualifying fasting TG value of ≥ 350 mg/dL. For subjects requiring a wash-out period, the Pre-Screening Visit will be their first study visit and will occur anywhere from 4 to 8 weeks prior to the Screening Visit (S1, Week -4) based on the type of lipid-regulating therapy and its associated duration of wash-out required.

The duration of the wash-out period will be dependent upon the status of the subject's current lipid-regulating therapy. Specifically, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors will require an 8-week wash-out period, fibrates will require a 6-week wash-out period, and niacin, OMG-3 compounds, bile acid sequestrants or other lipid-regulating therapies will require a 4-week wash-out period prior to the Screening Visit. If the subject needs to be washed off more than one lipid-altering medication; the medication that requires the longest washout period will be the default. If a potential subject is statin-naïve, or dosing only on a statin or ezetimibe (for at least 12 weeks) and not currently dosing on other lipid-altering medications, there is no requirement for a Pre-Screening Visit.

During this wash-out period, potential subjects will be counseled on the importance of maintaining a heart-healthy diet and limiting alcohol intake.

Screening Period: All potential subjects will participate in the Screening Period, including Screening Visit 1 (S1), Screening Visit 2 (S2) and, if necessary as outlined below, optional Screening Visit 3 (S3) up to 28 days prior to Study Day 1 (Visit T1). For potential subjects on stable statin therapy and/or ezetimibe for ≥ 12 weeks who do not require a wash-out period, S1 will be their first study visit. For other subjects who have been washing out their other lipid medications, S1 occurs after the full required washout has been completed.

During this Screening Period, potential subjects must meet the TG qualifying values in order to be eligible for randomization on Day 1 (Visit T1).

At the end of this 2-4-week diet and lifestyle stabilization and TG qualifying period, eligible subjects must have an average fasting TG level ≥ 500 mg/dL to < 1500 mg/dL in order to qualify for the 12-week double-blind treatment period. The TG level for qualification will be based on the average (arithmetic mean) of the Visit S1 and Visit S2 values. If a subject's average TG level from Visit S1 and Visit S2 falls outside the required range for entry into the study, one additional sample for fasting TG value can be collected 1 week later (at the Optional Visit S3), and the arithmetic mean from Visits S2 and S3 will then be used to determine eligibility.

Double-Blind Treatment Period: Eligible subjects will be randomized on Day 1 via an interactive web/voice response system (IWRS/IVRS) on Study Day 1 in a 1:1:1 ratio (30 subjects per group) to one of the following treatment groups:

- Gemcabene 300 mg QD, or
- Gemcabene 600 mg QD, or
- Placebo

Subjects will be stratified by baseline statin therapy (yes or no) and qualifying TG value (< 880 mg/dL or ≥ 880 mg/dL) to ensure background therapies and baseline TG values are balanced across all treatment groups.

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

8 ANALYSIS POPULATIONS

8.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who receive at least 1 dose of study drug and have at least 1 post-baseline efficacy assessment. All subjects in the FAS will be analyzed based on their randomized treatment group, regardless of the treatment they actually received. The FAS population will be the primary analysis population. All efficacy analyses will be performed on the FAS.

8.2 Per-Protocol Set

The Per Protocol Set (PPS) will be determined partially through sponsor review of blinded individual subject data and partially through objective criteria. Both methods will be completed prior to database lock. The following criteria for FAS subjects should be met in order to qualify for the PPS:

- Subjects completed the 12-week Treatment Period
- Subjects taking a statin in combination with study drug did not experience a change or interruption in statin dose
- Subjects took the same study drug medication for the entire study duration and it matches the treatment to which they were randomized

Additionally, a sponsor review for any other major protocol deviations that may impact efficacy (such as low study medication compliance [i.e., approximately 80% or lower] after Week 6) will be conducted, and further subjects could be excluded from the PPS. The PPS will be used to assess robustness of the analysis results. Subjects excluded from the PPS and the reason for exclusion will be provided in the listings.

8.3 Safety Analysis Set

The Safety Analysis Set (SAS) will include all randomized subjects who receive at least 1 dose of study drug. All subjects in the SAS will be analyzed based on the treatment group they actually received. All safety analyses will be conducted on the SAS.

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 Sample Size Computation

Approximately 90 subjects (30 subjects per treatment group) will be randomized into 1 of 3 treatment groups: gemcabene 300 mg, gemcabene 600 mg or placebo.

A sample size of 30 randomized subjects in the gemcabene 300 mg group, 30 randomized subjects in the 600 mg group and 30 randomized subjects in the placebo group is expected to provide 80% power to detect a difference of 35% in the percent change in TG from baseline to EOS between either of the gemcabene treatment groups and the placebo group. 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 43, and a drop-out rate of 15%.

In this Phase 2 study, both the gemcabene 300 mg and the 600 mg treatment groups will be compared to placebo separately using a 5% significance level ($\alpha = 0.05$). No statistical adjustment will be used for these two comparisons of the primary efficacy endpoint.

9.2 General Conventions

In general, categorical variables will summarized using frequency and percentages whereas mean, SD, median, minimum, and maximum will be used to summarize continuous variables.

For efficacy parameter values that are collected as "< x.x" or "> x.x", the numerical portion will be summarized, but the actual collected values will be reported in the listings. Safety results collected as "< x.x" or "> x.x" will not contribute to the summary tables, and will only be displayed in the listings.

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.

Change from baseline (CFBL) for a given parameter (eg, y) for a given subject 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. 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 last dose.

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 TG is defined as the average of the (Screening Visits ([S1 and S2] or [S2 and S3] occurring up to 28 days prior to Study Day 1) and Study Day 1 [pre-dose]) values. For subjects not requiring screening visit S3, the average of Screening Visits 1 and 2 and Study Day 1 (pre-dose), with each given equal weight, will be used. For subjects requiring screening visit S3, the average of Screening Visits 2 and 3 and Study Day 1 (pre-dose), with each given equal weight,will be used. If one of the screening visits is not completed and data were collected at a subsequent unscheduled visit, data from this visit will be used in the baseline calculation in place of the planned screening visit.
- Baseline for TC, non-HDL-C, HDL-C and VLDL-C is defined as the average of the last two pre-dose values (generally will be the average of Visit S2 and pre-dose Study Day 1/Visit T1). If one of the values that contribute to baseline (eg, the value from the Screening/Visit S1) is missing, the non-missing value will be used for baseline.
- Baseline for apolipoproteins (ie, Apo B, ApoA-I, ApoA-II, ApoC-II, ApoC-III, and ApoE), LDL-C (ultracentrifugation), LDL-TG, VLDL-TG, HDL-TG, hsCRP, IL-6, SAA, adiponectin, fibrinogen, ANGPTL4, fasting insulin levels, FPG, and HbA1c is defined as the value from pre-dose Study Day 1/Visit T1. If the value is missing on Day 1, the last non-missing value prior to first dose will be used.
- Baseline for ECGs, vital signs, visceral adiposity measures (BMI, waist circumference, 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/Visit T1 or prior) for the corresponding parameter.

Note that subjects have to be in a fasting state during an unscheduled visit in order for the unscheduled visit assessments to be considered for baseline calculations.

9.4 End of Study Definitions

EOS for the continuous primary, secondary, and exploratory parameters is defined as the average of the Week 10 and Week 12 values. If either the Week 10 or Week 12 value is missing, then the single value (Week 10 or Week 12) will be used. Completely missing values (both Week 10 and Week 12) will be imputed using last observation carried forward (LOCF), with the last on-treatment value carried forward as the EOS value. Note that study visits > 2 days after subject's last dose will not be considered (see Section 9.8).

9.5 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 safety analyses, observed cases 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. AEs missing relationship will be excluded from summaries of related AEs.

For AE start date, if only month and year are present, and they are the same month and year as the treatment start date, the day will be imputed by the treatment start day (and the AE will be considered treatment-emergent).

Rules for partial and missing dates for prior and concomitant medications 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 10 visit, it is assumed that the interruption occurred between the previous visit [eg, Week 6] and the Week 10 visit).

9.6 Interim Analysis

There are no planned interim analyses.

9.7 Treatment Misallocations

In instances where treatment is improperly allocated to a patient for the entire study or at any point during the study, efficacy data will be summarized and analyzed as randomized. Safety data will be summarized conservatively by the highest dose of actual treatment received, where lowest to highest dose is: placebo, Gemcabene 300 mg, Gemcabene 600 mg. For example, if a subject is randomized to Gemcabene 300 mg treatment group and the subject incorrectly takes Gemcabene 600 mg at any point during the study, all safety data for that subject will be analyzed in the Gemcabene 600 mg treatment group.

9.8 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 and other parameters scheduled to be measured post-randomization at only the Week 12 or ET Visit (ie, fasting insulin, FPG, HbA1c, ANGPLT4, adiponectin, lipoprotein size and particle number, waist circumference) will be summarized under the Week 12 Visit. If there is more than one value, the latest will be used. For efficacy, visits > 2 days after last dose will not be considered. For safety parameters analyzed by visit, visits > 5 days after last dose will not be considered.

Table 2. Visit Windows for Assessments Done at Day 1, Weeks 2, 6, 10, and 12[1]

Visit	Target Study Day	Visit Window
Day 1/Visit T1	1	Day 1

Table 2. Visit Windows for Assessments Done at Day 1, Weeks 2, 6, 10, and 12[1]

Visit	Target Study Day	Visit Window
Week 2/Visit T2	15	2, 29
Week 6/Visit T3	43	30, 57
Week 10/Visit T4	71	58, 78
Week 12/Visit T5	85	> 78

[1] For parameters not measured at Week 2/Visit T2 and Week 10/Visit T4, the Visit Window for Week 6/Visit T3 is (2, 64) while Week 12/Visit T5 is > 64. For parameters not measured at Week 2/Visit T2 and Week 6/Visit T3, the Visit Windows for Week 10/Visit T4 and Week 12/Visit T5 are (2, 78) and > 78, 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 and reasons for study discontinuation that occur post-randomization will be summarized by randomized treatment group (ie, placebo, gemcabene 300 mg and gemcabene 600 mg) for all randomized subjects, the FAS, and the SAS. 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 population. Additionally, demographic information will be presented by statin therapy (yes and no). 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
- Age group (18-44, 45-64, >=65)
- Height
- Weight
- BMI, and
- BMI group (<30 kg/m^2, ≥ 30 kg/m^2)

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

Age = integer ([Screening Visit date – 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 results will be listed for female subjects.

Baseline and stratification characteristics including the number and percentage of diabetic subjects, qualifying TG (<880 mg/dL, ≥ 880 mg/dL, randomized and actual) and subjects on and not on stable statin (randomized and actual) will be summarized. A subject on stable statin at baseline is defined as a subject with statin recorded on the Concomitant Medications CRF with a start date at least 12 weeks prior to first screening visit and a stop date on or after first dose (ie, medication stop date greater than or equal to day of first dose), or the medication is ongoing. Partial and missing dates will be imputed using rules in Appendix 2.

Baseline primary, secondary, and exploratory endpoints will be summarized for the FAS by randomized treatment group and overall. Specifically, the following parameters will be summarized at baseline: lipids, apolipoproteins, lipoprotein size and particle number, inflammatory and other biomarkers, and visceral adiposity measures.

This table will be repeated by randomized baseline statin stratum (yes or no), baseline qualifying TG stratum, and diabetes status.

CI [redacted]

For categorical parameters, denominators for percentages will be the number of subjects in the corresponding treatment 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. 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) as (number of tablets taken since last visit/number of tablets that should have been taken since last visit)*100. Treatment period is defined as the time period from first dose date to last dose date. As each subject is instructed to take 2 tablets per day during the treatment period, the number of tablets that should have been taken since the last visit will be computed as 2 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) for the second visit (Week 2 or ET), and (day of visit - day of last visit) for all subsequent visits (up to Week 12). Compliance will be summarized by visit by 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 2 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 (n, mean, median SD, minimum, maximum for overall compliance, and frequencies and percentages for categories of compliance) 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 (n, mean, median, SD, minimum, maximum). 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, duration of exposure minus days when the study medication was interrupted). Number of days on treatment and number of days study medication was interrupted will also be summarized for the SAS.

11 EFFICACY PARAMETERS

11.1 Primary Analysis

The primary efficacy endpoint (percent change in fasting serum TG from baseline to EOS) will be analyzed using ANCOVA on rank-transformed data (i.e., ranked ANCOVA) with percent change from baseline to EOS in TG (converted to ranks) as the dependent variable; treatment and baseline statin (yes or no) as factors; and ranked baseline fasting serum TG as a covariate. The ranked ANCOVA is used due to the expected non-normality historically observed with triglyceride data. The primary analysis will be performed using the FAS. The null hypotheses to be tested are the following:

- H_1: there is no difference in the percent CFBL to EOS in fasting serum TG between gemcabene 300 mg and Placebo
- H_2: there is no difference in the percent CFBL to EOS in fasting serum TG between gemcabene 600 mg and Placebo

A 2-sided test with a significance level of 0.05 will be used for the comparison of the gemcabene 300 mg and 600 mg groups separately to the placebo group. No statistical adjustment will be performed for multiplicity in this Phase 2 study. Note that EOS is defined using LOCF as indicated in Section 9.4. The median, interquartile range, and associated p-value from the ranked ANCOVA will be presented for each treatment group.

```
proc glm data=data;
    class TRT(ref="Placebo") Statin;
    model r_pctCFBL = TRT Statin r_Base / solution;
    lsmeans TRT / stderr pdiff;
run;
```

Where a ranked ANCOVA is used, ranking will be done on the outcome variable and baseline covariate. All values will be ranked by visit regardless of treatment group, with ties receiving the average of the ranks.

Ranked ANCOVA is generally used when the statistical assumptions for parametric ANCOVA, including normality and homoscedasticity (equal variances), are not met, therefore these formal assumptions will not be checked for the ranked ANCOVA analyses. The assumption of homogeneity of regression slopes across treatment groups (parallel slopes) will be investigated by including the interaction between baseline fasting serum TG and treatment group in the model explicated previously. If results indicate that the interaction between baseline fasting serum TG and treatment group is not significant, the assumption of parallel slopes will be considered met. If the assumption of parallel slopes is clearly violated, the final model may be adjusted.

Although qualifying TG (> 880 mg/dL or ≤ 880 mg/dL) is a stratification variable, it will not be included in the primary model or any model with TG as the dependent variable, since baseline TG (ranked) is already included in these models as a covariate. Baseline TG and qualifying TG stratum are expected to be highly correlated and could lead to multicollinearity and variance inflation within the model. Therefore, only ranked baseline TG will be used to adjust for TG.

Placebo-corrected median TG change from baseline to EOS estimates (Gemcabene 300 mg vs Placebo; and Gemcabene 600 mg vs Placebo) as well as their corresponding 95% confidence intervals will be obtained using the Hodges-Lehmann Estimate.

Descriptive statistics will also be provided by visit.

11.2 Sensitivity Analysis

A sensitivity analysis of the primary LOCF analysis will be performed using the same ranked ANCOVA as the primary analysis, only for this analysis, all subjects from the FAS who discontinued early will be assigned the lowest available rank. All such subjets will be assigned the same value and thus the same rank will be assigned (i.e., treating each subject as a tie). The ranked ANCOVA will then be performed on this dataset. An estimate of the placebo-corrected median difference will not be provided for this analysis.

An additional sensitivity analysis will be conducted by repeating the primary analysis on the PPS population.

11.3 Secondary Analysis

Secondary analyses will be conducted using the methodology detailed below. All secondary analyses will be conducted using the FAS population (or the specific subgroup within the FAS population, eg, diabetic subjects).

The secondary endpoints are as follows:

- CFBL and percent CFBL to Weeks 2, 6, 10, 12, and EOS in fasting serum TG;
- CFBL and percent CFBL to Weeks 2, 6, 10, 12, and EOS in TC, non-HDL-C, HDL-C, and VLDL-C;
- CFBL and percent CFBL to Weeks 10, 12, and EOS in LDL-C LDL-TG, VLDL-TG, HDL-TG;
- CFBL and percent CFBL to Weeks 10, 12, and EOS in Apo B, ApoA-I, ApoA-II, ApoC-II, ApoC-III, and ApoE;
- CFBL and percent CFBL to Week 12 in lipoprotein size and particle number (NMR);
- CFBL and percent CFBL to Weeks 10, 12, and EOS in hsCRP, IL-6, SAA, adiponectin, and fibrinogen; and
- Percent of subjects achieving a TG value < 500 mg/dL (5.65 mmol/L) at Weeks 10, 12, and EOS.

Continuous secondary efficacy endpoints that measure CFBL and percent CFBL will be analyzed using ranked ANCOVA with CFBL or percent CFBL in the respective parameter as the dependent variable; treatment, baseline statin (yes or no) and qualifying TG stratum (> 880 mg/dL or ≤ 880 mg/dL) as factors; and the respective ranked baseline as a covariate. Qualifying TG stratum will not be included as a factor in secondary ANCOVA models where TG is the parameter of interest (dependent variable). For the EOS time point, EOS is defined in Section 9.4 or all other time points, missing values will be imputed using LOCF, with the last on-treatment value carried forward to that time point.

Secondary efficacy endpoints that are continuous will be analyzed using ranked ANCOVA and secondary efficacy endpoints that are binary will be analyzed using logistic regression.

The output from each ranked ANCOVA will be consistent with the primary efficacy model.

The percent of subjects achieving a TG value < 500 mg/dL (5.65 mmol/L) at Weeks 10, 12, and EOS will be analyzed using a logistic regression with treatment, baseline statin use (yes or no), and baseline TG value as independent factors. The percent of subjects in each treatment group achieving a TG value < 500 mg/dL, and the odds ratios (ORs) with 95% confidence intervals and p-values will be presented to compare gemcabene 300 mg and gemcabene 600 mg separately with the placebo group.

The SAS code used to conduct a logistic regression model is provided below:

```
proc logistic data=data;
      class TRT(ref="Placebo") Statin;
      model Outcome(event="event")= TRT Statin Base / expb;
run;
```

Descriptive statistics for all secondary efficacy parameters will also be provided by visit.

11.4 Exploratory Analysis

CI

CI [redacted]

[redacted]

Descriptive statistics will also be provided by visit

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 randomized treatment group. All safety data will be presented in listings.

12.1 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. All AE tables will be summarized for overall by treatment group and by stable statin use at baseline (according to the CRF) within treatment group. 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 start date on or after the first dose date and less than 30 days after the last dose date. If 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, and treatment group within each baseline statin (yes or no):

- Number of subjects with at least one TEAE, drug-related TEAE, SAE, drug-related SAE;
- Number of subjects who discontinued study treatment due to TEAE, drug-related TEAE, SAE, and drug-related SAE;
- Number of subjects who discontinued the study due to a TEAE; and
- Number of subjects who had a study treatment interruption due to a TEAE;
- 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 descending PT ;
- TEAEs by SOC, PT, and maximum severity;
- Related TEAEs by SOC and PT;

- Related TEAEs by descending PT;
- SAEs by SOC and PT;
- Related SAEs by SOC and PT;
- TEAEs leading to treatment discontinuation by SOC and PT;
- Related TEAEs leading to treatment discontinuation 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 total column for the gemcabene 600 mg group, followed by the 300 mg group, then placebo.

Note that the overview of AEs will be provided separately for the double-blind treatment period and follow-up period, to allow for a delivery of the double-blind data only during the database freeze.

If a subject has more than one 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 one 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 one 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.

12.2 Clinical Laboratory Assessments

The laboratory parameters below will be summarized at baseline and at each post-baseline time point by treatment group, using the SAS. CFBL to each time point including end of treatment for each of the following laboratory parameters will also be summarized by treatment group.

Chemistry: alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (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), cystatin-C

Hematology: hemoglobin, hematocrit, leukocytes, basophils, eosinophils, lymphocytes, monocytes, neutrophils, platelets, red blood cell count, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular volume

Coagulation: prothrombin time, activated partial thromboplastin time, international normalized ratio

Urinalysis: pH, specific gravity, NGAL, creatinine, protein, protein/creatinine ratio, albumin, albumin/creatinine ratio

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 (eg, <XX.X), the value will not contribute to summary statistics but will be included in the listings.

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. Percentages will be based on the number of subjects in each category at baseline.

Potentially clinically significant out-of-range values will also be summarized for safety laboratory parameters. The potentially clinically significant (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. Summaries will consider any time post-baseline. The denominator for a given percentage will be the number of subjects who are eligible for each criterion (eg, had a post-baseline assessment or had consecutive post-baseline assessments for the corresponding parameter). Additionally, for subjects with post-baseline chemistry laboratory values meeting the PCS criteria at consecutive visits, all laboratory values (including urinalysis parameters) will be provided in a listing.

Table 3. Lab PCS Criteria

Laboratory Parameter	Unit	PCS Criteria
ALT	U/L	> 2 × ULN
ALT	U/L	> 3 × ULN
AST	U/L	> 2 × ULN
AST	U/L	> 3 × ULN
BUN	mg/dL	> 2 × ULN
Creatine kinase	U/L	> 3 × ULN
Creatine kinase	U/L	> 5 × ULN
Creatinine	mg/dL	> 0.3 increase from baseline
Estimated GFR	mL/min	Decrease > 15 mL/min from baseline
Hemoglobin	g/dL	Decrease > 1.5 from baseline
Urinalysis Parameter	**Unit**	**PCS Criteria**
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.

Additionally, urinalysis parameters that are not 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.

12.3 ECGs

ECGs will be performed in triplicate at the Screening Visit, Day 1, Week 2, Week 6, Week 10, 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 QT interval corrected for heart rate with Bazett's formula (QTcB) and using QT interval corrected for heart rate with Fridericia's formula (QTcF), and T-wave amplitude. The average of the non-missing values for a given ECG parameter (eg, heart rate) will be used for analysis. In cases where only one ECG is performed, the result of the single ECG will be used. 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 criteria (see Table 4). The number and percent of subjects meeting the criteria below will be summarized by treatment group using the SAS. 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), systolic blood pressure (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 using the SAS.

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 using the SAS. The denominator used to calculate the percentage will be the number of subjects that underwent a physical examination at the corresponding visit.

12.6 Plasma Concentrations of Gemcabene

The concentration of gemcabene will be obtained from reserve plasma samples. Plasma concentration of gemcabene will be summarized using descriptive statistics and presented in a listing.

13 OTHER RELEVANT DATA ANALYSES/SUMMARIES

13.1 Medical and Surgical 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 600 mg column, then the gemcabene 300 mg 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 of study drug (ie, medication stop date less than date of first dose of study drug). A concomitant medication is defined as a medication with a start date on or before the date of the subject's last dose of study drug (ie, medication start date less than or equal to date of last dose of study drug) and a stop date on or after the date of the subject's first dose of study drug (ie, medication stop date $\geq$ date of first dose of study drug);

thus, a medication that is ongoing at the time of the subject's first dose of study drug 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 taken within the period after last dose date and follow-up visit will not be summarized in the tables, but will be included in the concomitant medications listing. Medications will be summarized by ATC level 3 (level 3 indicates the therapeutic/pharmacologic subgroup) alphabetically and preferred name (decreasing frequency in the gemcabene 600mg column, then gemcabene 300 mg column within each ATC) by randomized 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.

13.3 Concomitant Procedures

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 less than or equal to date of last dose) and a stop date on or after the date of the subject's first dose (ie, procedure stop date greater than or equal to date of first dose). Concomitant procedures will be presented in a listing containing verbatim terms for the SAS.

14 APPENDICES

Appendix 1. Schedule of Assessments and Procedures

	Pre-Screening[a]	Screening[b,f]				Treatment Period[c]				Follow-Up[d]	ET
		Study Day -28 to -21	Study Day -14 to -7	Study Day-7	Study Day 1[e]	Week 2/ Study Day 15 ± 3 days	Week 6/ Study Day 43 ± 3 days	Week l0/ Study Day 71 ± 3 days	Week 12/ Study Day 85 or up to 3 days prior to Study Day 85	Study Day 113	
	Visit Identifier	Visit S1	Visit S2	Visit S3	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5	Visit FU1	
Informed consent	X	X									
Inclusion/exclusion criteria	X	X	X	X	X						
Medical/surgical history and demographics	X	X	X	X	X						
Full physical examination[g]	X	X							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	X		X
Body Mass Index (BMI)	X	X			X			X	X		X
Waist circumference					X				X		X
Urinalysis + NAGL[l]	X	X			X		X		X	X[i]	X
Protein:creatinine ratio; albumin:creatinine ratio	X	X			X		X		X	X[i]	X
Serum/urine pregnancy test[m]	X	X			X	X	X	X	X	X[i]	X
Safety chemistry panel, coagulation, and hematology[n]	X	X	X	X	X	X	X	X	X	X[i]	X
TSH and serology[o]	X	X[f]									
Fasting lipid panel[p]	X[q]	X	X	X	X	X	X	X	X		X
Fasting apolipoproteins[r]					X			X	X		X
LDL-C ultracentrifugation (LDL-C, LDL-TG, VLDL-TG)					X			X	X		X
CI [redacted]					X				X		X

Appendix 1. Schedule of Assessments and Procedures

	Pre-Screening[a]	Screening[b,f]				Treatment Period[c]				Follow-Up[d]	ET
		Study Day -28 to -21	Study Day -14 to -7	Study Day-7	Study Day 1[e]	Week 2/ Study Day 15 ± 3 days	Week 6/ Study Day 43 ± 3 days	Week l0/ Study Day 71 ± 3 days	Week 12/ Study Day 85 or up to 3 days prior to Study Day 85	Study Day 113	
	Visit Identifier	Visit S1	Visit S2	Visit S3	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5	Visit FU1	
HbA1c	X	X			X				X		X
Cystatin-C, ANGPTL4, adiponectin					X				X		X
hsCRP, SAA, IL-6, and fibrinogen					X			X	X		X
Lipoprotein size and particle number					X				X		X
Randomization					X						
Study drug administration[s]					X	X	X	X			
Dispense study drug and instructions					X	X	X	X			
Compliance check						X	X	X	X		X
Distribute drug diary					X	X	X	X			
Dietary assessment (self-reported)[t]	X	X	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	X	X
Concomitant medications	X	X[f]	X	X	X	X	X	X	X	X	X
Reserve serum samples[w]					X	X	X	X	X		X
Reserve plasma PK samples[x]					X	X	X	X	X		X
Collect drug diary						X	X	X	X		X
Reserve genotyping sample					X						

Apo = apolipoprotein; 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; TC = total cholesterol; TG = triglyceride;

Appendix 1. Schedule of Assessments and Procedures

	Pre-Screening[a]	Screening[b,f]				Treatment Period[c]				Follow-Up[d]	ET
		Study Day -28 to -21	Study Day -14 to -7	Study Day-7	Study Day 1[e]	Week 2/ Study Day 15 ± 3 days	Week 6/ Study Day 43 ± 3 days	Week l0/ Study Day 71 ± 3 days	Week 12/ Study Day 85 or up to 3 days prior to Study Day 85	Study Day 113	
	Visit Identifier	Visit S1	Visit S2	Visit S3	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5	Visit FU1	

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, PCSK9 inhibitors will require an 8-week Wash-Out Period, fibrates will require a 6-week Wash-Out Period, and niacins, OMG-3, bile acid sequestrants or other lipid-regulating therapies 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 28 days prior to Study Day 1. For subjects taking the required stable statin therapy for > 12 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 Study Day 1 through Week 10. Week 12 assessments can be performed up to 3 days prior to Study Day 85, but not after Study Day 85.

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 Study 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 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. Urine will be collected for a full urinalysis at the lab including protein:creatinine ratio and albumin:creatinine ratio at the Prescreening/screening Visit, Study Day 1, Week 6, 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 Study Day 1, Week 6, Week12, 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, Study Day 1, Week 2, Week 6, and Week 10.

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

Appendix 1. Schedule of Assessments and Procedures

	Pre-Screening[a]	Screening[b,f]				Treatment Period[c]				Follow-Up[d]	ET
		Study Day -28 to -21	Study Day -14 to -7	Study Day-7	Study Day 1[e]	Week 2/ Study Day 15 ± 3 days	Week 6/ Study Day 43 ± 3 days	Week l0/ Study Day 71 ± 3 days	Week 12/ Study Day 85 or up to 3 days prior to Study Day 85	Study Day 113	
	Visit Identifier	Visit S1	Visit S2	Visit S3	Visit T1	Visit T2	Visit T3	Visit T4	Visit T5	Visit FU1	

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.

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.

p. Includes non-HDL-C, TC, TG, HDL-C, VLDL-C and HDL-TG. 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, black tea or black coffee.

q. Includes 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, black tea or black coffee.

r. Includes ApoB, ApoA-I, ApoA-II, ApoC-II, ApoC-III, and ApoE. 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 Study Day 1. Subjects will self-dose at all other times during the Treatment Period.

t. Subjects will self-report compliance to a stable, heart-healthy diet.

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 (Study Day 1) should be reported as an update to medical history as well as be reported on the appropriate adverse event eCRF.

w. The following may be analyzed: RLP-C, RLP-TG and RLP-apoB, Lp(a), ox-LDL, and Lp-PLA2.

x. Plasma samples collected at Week 2, Week 6, Week 10, Week 12 and ET will be used for the analysis of gemcabene PK. The plasma sample collected at Day 1 will be reserve.

Appendix 2. Prior and Concomitant Medications 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 Anti-diabetes Pharmacologic Therapy

The WHO Drug Dictionary version 01 Mar 2016 was used to identify the following ATC categories and descriptions which will be used to identify anti-diabetes pharmacologic therapy.

ATC3/ATC3 Description[1]	ATC4/ATC4 Description
A10A/INSULINS AND ANALOGUES	A10AB/Insulins and analogues for injection, fast-acting
A10A/INSULINS AND ANALOGUES	A10AC/Insulins and analogues for injection, intermediate-acting
A10A/INSULINS AND ANALOGUES	A10AD/Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting
A10A/INSULINS AND ANALOGUES	A10AE/Insulins and analogues for injection, long-acting
A10A/INSULINS AND ANALOGUES	A10AF/Insulins and analogues for inhalation
A10B/ BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	A10BA/Biguanides
A10B/ BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	A10BB/Sulfonylureas
A10B/ BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	A10BC/Sulfonamides (heterocyclic)
A10B/ BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	A10BD/Combinations of oral blood glucose lowering drugs
A10B/ BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	A10BF/Alpha glucosidase inhibitors
A10B/ BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	A10BG/Thiazolidinediones
A10B/ BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	A10BH/Dipeptidyl peptidase 4 (DPP-4) inhibitors
A10B/ BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	A10BX/Other blood glucose lowering drugs, excl. insulins
A10X/OTHER DRUGS USED IN DIABETES	A10XA/Aldose reductase inhibitors

ATC = anatomical therapeutic chemical, DPP = dipeptidyl peptidase

[1] All medications listed have ATC1/ATC1 Description = A/ALIMENTARY TRACT AND METABOLISM and ATC2/ATC2 Description = A10/DRUGS USED IN DIABETES.