AstraZeneca

Statistical Analysis Plan

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A Randomised, Double-blind, Placebo controlled, Parallel Group, Phase III Long-term Study to Evaluate Efficacy and Safety of 12 Weeks and 52 Weeks of AZD0585 Administration, Respectively, in Patients with Hyperlipidemia Accompanied by Hypertriglyceridemia (TG in the Range 150-499 mg/dL)

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Date

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Global Product Statistician [redacted] Sept 20, 2016
Date

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AA	Arachidonic acid
AE	Adverse Event
ALP	Alkaline phosphatise
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo	Apo-lipoprotein
AST	Aspirate transferase
AT	Aminotransferase; short for ALT or AST
BMI	Body Mass Index
CI	Confidence Interval
DAE	AE leading to Discontinuation
DHA	Docosahexaenoic Acid
ECG	Electrodiagram
EPA	Eicosapentaenoic Acid
FAS	Full Analysis Set
HDL-C	High-density lipoprotein cholesterol
hs-CRP	High-sensitivity C-reactive protein
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
LS	Least squares
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multipile imputation
MMRM	Mixed model with repeated measures
OC	Observed Case
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Protocol Deviation
PT	Preferred Term
QTcF	QT interval corrected by Fridericia Formula ($= QT / \sqrt[3]{RR}$)

Abbreviation or special term	Explanation
RLP-C	Remnant lipoprotein cholesterol
SAE	Serious Adverse Event
SMQ	Standard MedDRA Query
SOC	System Organ Class
TBIL	Total bilirubin
TC	Total cholesterol
TG	Triglyceride
ULN	Upper limits of normal
VLDL-C	Very-low-density lipoprotein cholesterol

AMENDMENT HISTORY

Date	Brief description of change
19Sep2016	Concomitant medications: summary of all prior/concomitant medications are changed to summary of all prior/concomitant medications excluding lipid lowering medications. Adverse events: the following two summaries are now taken out based on consideration of relevance for study report. - Most common AEs (i.e., reported by ≥ 2 % of subjects in any treatment group based on Preferred Terms) - AEs by treatment period (by Day 1-84, Day 85-168, Day 169-252, Day 253-336, Day 337- end of study)

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objectives

Primary Objective:	Outcome Measure:
To demonstrate the short-term (up to 12 weeks) efficacy of AZD0585 2 g and 4 g compared to Placebo (corn oil) in Japanese patients with hyperlipidemia accompanied by hypertriglyceridemia (TG in the range 150-499 mg/dL)	Placebo-corrected percent change in serum TG level from baseline to Week 12 Endpoint.
To evaluate the long-term (up to 52 weeks) safety of AZD0585 administration in patients with hyperlipidemia accompanied by hypertriglyceridemia (TG in the range 150-499 mg/dL)	Adverse events, brief physical findings/clinical assessments, ECG assessments, vital signs and laboratory evaluations.

1.1.2 Secondary objectives

Secondary Objective:	Outcome Measure :
To assess the effect of each dose of AZD0585 on fasting serum lipid profile	Percent change in each serum lipid level from baseline to Week 12 Endpoint in serum lipid profile including total cholesterol (TC), LDL-C, VLDL-C, HDL-C and non-HDL-C.
To assess the effects of each dose of AZD0585 in parameters shown as outcome measure for the objective	• Apolipoprotein (Apo) A-I, Apo A-II, Apo B, Apo B48, Apo C-II, Apo C-III, and Apo E based on percent changes from baseline to Week 12. • Plasma fatty acids profile: EPA, DHA, AA and EPA/AA ratio up to Week 12. • Small dense LDL and LDL-C/Apo B ratio based on percent changes from baseline to Week 12. • Lp(a), RLP-C, PCSK9 and hs-CRP up to Week 12.

1.1.3 Exploratory objectives

Exploratory Objective:	Outcome Measure :
To assess the time-course of efficacy-related parameters profile up to Week 52 and explore the efficacy characteristics of long-term use of AZD0585 2 g/4 g vs. Placebo.	• Fasting serum lipid profile including TG, TC, LDL-C, VLDL-C, HDL-C and non-HDL-C. • Apo A-I, Apo A-II, Apo B, Apo B48, Apo C-II, Apo C-III, and Apo E. • Plasma fatty acids profile: EPA, DHA, AA, and EPA/AA ratio. • Small dense LDL and LDL-C/Apo B ratio. • Lp(a), RLP-C, PCSK9 and hs-CRP.

1.2 Study design

This is a randomised, double-blinded, placebo controlled, study employing 3 arm parallel groups to evaluate efficacy of 12 weeks and safety of 52 weeks of AZD0585 administration in patients with hyperlipidemia accompanied by hypertriglyceridemia (TG in the range 150-499 mg/dL).

Total 375 subjects will be randomised to 3 cohorts, A) Placebo, B) AZD0585 2 g, and C) AZD0585 4 g, at a ratio of 1:2:2, respectively. The efficacy will be evaluated as placebo-corrected percent change TG reduction at 12 weeks from the baseline TG level. The safety will be evaluated as adverse events and other safety parameters (vital sign, clinical laboratory test, etc) during 52-week treatment period.

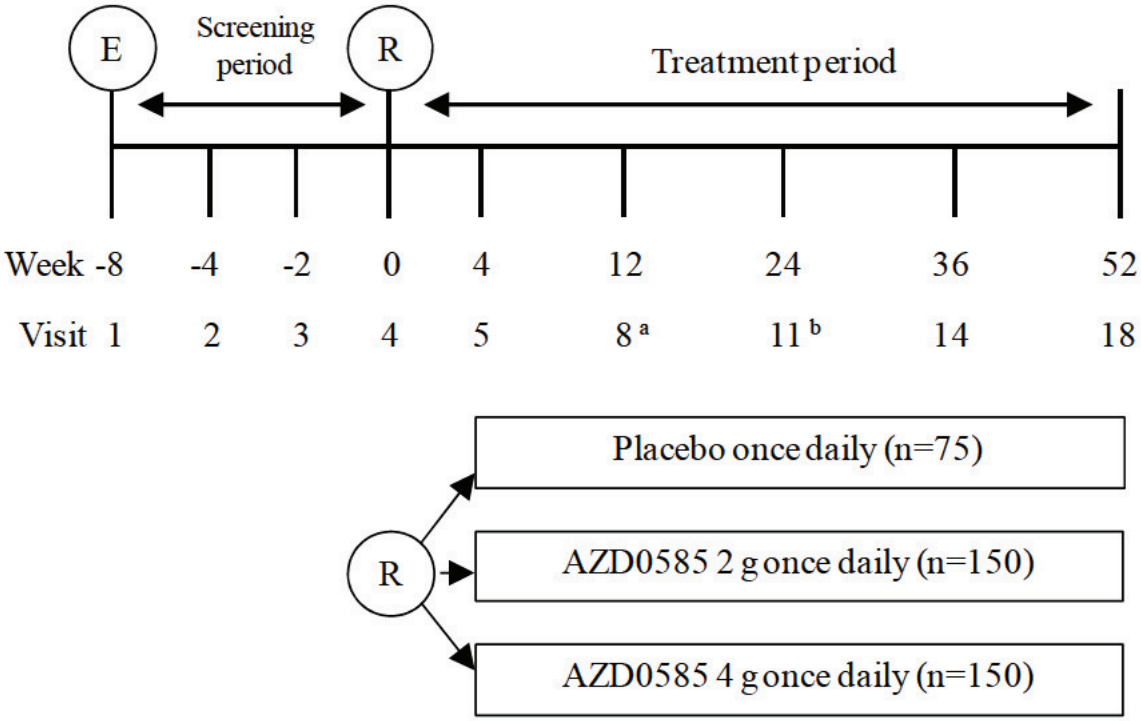
A. Placebo (corn oil) 4 g once daily (n=75)
B. AZD0585 2 g (+placebo 2g) once daily (n=150)
C. AZD0585 4 g once daily (n=150)

Randomisation will be stratified by the following factors to ensure equal representation across all treatment groups;

- Current use of statin (yes vs. no) at baseline
- Baseline TG level <300 or ≥300 mg/dL

In addition to the stratified randomisation the recruitment of patients will monitored so that approximately 50% of total randomised patients are statin users.

Figure 1 Study flow chart



E : Enrolment, R : Randomisation

a An efficacy primary analysis will be done at Visit 8.
b The data of interim analysis will be cut off when last subjects comes by Visit 11. An interim analysis will include all patients' data available until data cut-off, including primary/secondary analysis at Week 12 Endpoint for efficacy as well as safety evaluation based on 24-week or longer exposure to study drug.

1.3 Number of subjects

A common standard deviation of 24% is assumed for primary efficacy variable (Percent change from baseline to Week 12 Endpoint in serum TG). 150 patients in both of AZD0585 2 g and AZD0585 4 g and 75 patients in Placebo will ensure the power for detecting 12.5% difference of AZD0585 each dose vs. Placebo to be at least 92%, based on t-test with two-sided significance level of 0.05/2= 0.025, where approximate normality is assumed for the primary efficacy variable and significance level is conservatively adjusted for multiplicity for two comparisons by Hochberg procedure.

In the above calculation, it was assumed that a total of 375 patients are to be randomised to Placebo, AZD0585 2 g, AZD0585 4 g with ratio of 1:2:2 and that proportion of randomised patients not contributing primary analysis at Week 12 endpoint is negligible.

In addition, the above sample size is expected to be sufficient to provide long term safety data of more than 100 Japanese patients treated by AZD0585 2 g or by AZD0585 4 g for as long as

1 year assuming 10-15% drop out rate during 52-week treatment period, in accordance with Japan regulatory requirement.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Randomised set: all patients who received randomisation number.

Full Analysis Set (FAS): all randomised set who had both any baseline and any post-baseline efficacy measurements. Patients will be analyzed according to their randomised treatment. FAS will be considered primary analysis set used for all efficacy evaluation.

Per Protocol Set (PPS): all patients in FAS who completed the first 12-week treatment period without any significant protocol deviations affecting primary efficacy evaluations. All criteria to exclude patients from the PPS will be made prior to the unblinding of the study. Patients will be analyzed according to their randomised treatment. Analyses on PPS will be of supportive purpose and limited to primary and important efficacy variables. Per Protocol Set will be subset of FAS, typically including patients without any important protocol deviations listed in Table 1.

Safety Analysis set (SAF): all patients who took at least on dose of double-blind study medication. Patients will be analyzed according to the actual study medication received. If a patient has received different study medications, the study physician and the clinical team will determine treatment group on a case-by-case basis, prior to unblinding.

2.2 Violations and deviations

Protocol deviations will be reviewed in a blinded fashion by the study team prior to database lock. The important protocol deviations which lead to exclusion from Per-protocol analysis are listed in the Table 1. All decisions to exclude subjects and/or data from the Full Analysis Set to form the Per-Protocol Analysis Set will be agreed by the study team and documented prior to the unblinding of the study.

Table 1 List of important protocol deviations

#	Protocol deviations
1	Discontinued study before attending 12-week visit
2	Subjects who took wrong study medication during initial 12-week treatment period
3	Subjects who were not compliance to study drug (< 80% or > 120%) during the initial 12-week treatment period
4	Subjects who changed the dose/regimen of statin during the initial 12-week treatment period

#	Protocol deviations
5	Subjects who newly introduced additional lipid lowering drugs/supplements during the initial 12-week treatment period

3. ANALYSIS VARIABLES

3.1 Primary Efficacy variable

Primary efficacy variable is percent change from baseline to the Week 12 Endpoint in serum triglyceride (TG).

3.2 Secondary efficacy variables

Secondary efficacy variables are listed below.

3.2.1 Fasting lipids

- Percent change from baseline to the Week 12 Endpoint in total cholesterol (TC)
- Percent change from baseline to the Week 12 Endpoint in high-density lipoprotein-cholesterol (HDL-C)
- Percent change from baseline to the Week 12 Endpoint in non- high-density lipoprotein-cholesterol (non-HDL-C)
- Percent change from baseline to the Week 12 Endpoint in very-low-density lipoprotein-cholesterol (VLDL-C)
- Percent change from baseline to the Week 12 Endpoint in low-density lipoprotein-cholesterol (LDL-C)

3.2.2 Secondary variables other than fasting lipids

- Percent change from baseline to Week 12 in Apo-lipoprotein A-I (Apo A-I)
- Percent change from baseline to Week 12 in Apo-lipoprotein A-II (Apo A-II)
- Percent change from baseline to Week 12 in Apo-lipoprotein B (Apo B)
- Percent change from baseline to Week 12 in Apo-lipoprotein B48 (Apo B48)
- Percent change from baseline to Week 12 in Apo-lipoprotein C-II (Apo C-II)
- Percent change from baseline to Week 12 in Apo-lipoprotein C-III(Apo C-III)
- Percent change from baseline to Week 12 in Apo-lipoprotein E (Apo E)
- Percent change from baseline to Week 12 in Eicosapentaenoic Acid (EPA)
- Percent change from baseline to Week 12 in Docosahexaenoic Acid (DHA)
- Percent change from baseline to Week 12 in Arachidonic acid (AA)
- Percent change from baseline to Week 12 in EPA/AA ratio

- Percent change from baseline to Week 12 in Small dense LDL
- Percent change from baseline to Week 12 in LDL-C/Apo B ratio
- Percent change from baseline to Week 12 in Lipoprotein(a) (Lp(a))
- Percent change from baseline to Week 12 in Remnant Lipoprotein Cholesterol (RLP-C)
- Percent change from baseline to Week 12 in Proprotein convertase subtilisin/kexin type 9 (PCSK9)
- Percent change from baseline to Week 12 in High-sensitivity C-reactive protein (hs-CRP)

3.3 Exploratory efficacy variables

Exploratory efficacy variables are time course from baseline to Week 52 of following variables.

- Fasting serum lipid profile including TG, TC, LDL-C, VLDL-C, HDL-C and non-HDL-C
- Apo A-I, Apo A-II, Apo B, Apo B48, Apo C-II, Apo C-III, and Apo E
- Plasma fatty acids profile: EPA, DHA, AA, and EPA/AA ratio
- Small dense LDL and LDL-C/Apo B ratio
- Lp(a), RLP-C, PCSK9 and hs-CRP

3.4 Primary Safety variables

Safety of AZD0585 2g/4g treatment will be analyzed when administered for up to 52 weeks. The safety evaluations will include analyses of:

- Adverse events
- (Safety) Laboratory parameters
- Electrodiagram (ECG)
- Vital signs
- Physical examination and findings

4. ANALYSIS METHODS

4.1 General principles

4.1.1 Objectives and hypotheses

4.1.1.1 Primary Efficacy Objective

The primary efficacy objective of this study is to demonstrate the efficacy of AZD0585 2 g and 4 g when compared with Placebo using the percent change from baseline in TG to Week 12 Endpoint as a primary efficacy variable.

The null hypothesis H_{01}, H_{02} given below will be tested against the alternative hypothesis H_{A1}, H_{A2}.

H_{01}: $\mu_{E2} - \mu_P = 0$, H_{02}: $\mu_{E4} - \mu_P = 0$

H_{A1}: $\mu_{E2} - \mu_P \neq 0$, H_{A2}: $\mu_{E4} - \mu_P \neq 0$

where μ_{E2}, μ_{E4}, μ_p denote true means of AZD0585 2g, AZD0585 4g, Placebo respectively.

In order to protect family wise error rate (FWER) to be 5%, superiority of AZD0585 2 g vs. Placebo and superiority of AZD0585 4 g vs. Placebo will be tested based on Hochberg procedure using two-sided significance level of 0.05. If a p-value for each hypothesis is less than 0.05/2 = 0.025, the corresponding hypothesis claimed to be demonstrated. If both p-values (for 2g and 4g dose groups) are less than 0.05, then the both hypotheses are claimed to be demonstrated.

All analyses other than analysis of the primary efficacy endpoint will be interpreted descriptively. Consequently, no adjustments for multiplicity will be necessary for such analyses. Ninety-five percent confidence intervals will be calculated, where appropriate, as measures of study precision. P-values may be calculated but are to be regarded as descriptive.

4.1.1.2 Primary Safety Objective

The other primary objective is to evaluate the safety of long-term (up to 52 weeks) treatment by AZD0585 2g and AZD0585 4g. No formal statistical hypothesis test will be carried out for this safety primary objective.

4.1.2 Definitions

4.1.2.1 Baseline

For fasting lipids (TG, TC, HDL-C, non-HDL-C, VLDL-C, and LDL-C), baseline is defined as an average of week -4, week -2 (, week -1 if patients attended Visit 3a) and week 0 measurements.

For the other efficacy parameters listed in section 3.2.2 as well as safety parameters, baseline value is defined as the last non-missing assessment on or prior to the date of the first dose of the study medication. In typical case, week 0 is considered as baseline.

4.1.2.2 Endpoints

For fasting lipids (TG, TC, HDL-C, non-HDL-C, VLDL-C, and LDL-C), the Week 12 Endpoint is defined as an average of week 10 and week 12 measurements. For discontinued subjects, average of last non-missing two consecutive measurements up to week 12 is used as the week 12 Endpoint. If only a single measurement is available for a patient, it is used as the week 12 Endpoint.

For the other secondary efficacy parameters listed in section 3.2.2, if no measurement is available at Week 12, the last post-baseline single measurement up to Week 12 will be used if appropriate. Such cases will be presented as Week 12 (LOCF).

For any variables, last non-missing measurement up to Week 24/52 will be employed for Week 24/52(LOCF) evaluation if appropriate.

4.1.2.3 Percent change from baseline and change from baseline

Percent change from baseline to any Week t (protocol-planned visits or Endpoints as defined section 4.1.2.2) is defined as follows:

$$P_{Week\ t} = 100 \times (M_{Week\ t} - M_{baseline}) / M_{baseline}\ .$$

where:

- $P_{Week\ t}$ is the percent change from baseline at Week t,
- $M_{Week\ t}$ is the measurement at Week t,
- $M_{baseline}$ is the measurement at baseline as defined in section 4.1.2.1.

Change from baseline to any Week t (or Endpoints) is defined as follows *:*

$$C_{Week\ t} = M_{Week\ t} - M_{baseline}\ .$$

where $C_{Week\ t}$ is the change from baseline at Week t, and $M_{Week\ t}$ and $M_{baseline}$ are as defined above.

4.1.2.4 Study Day

Study Day is calculated from date of first dose of double-blind medication. The first dose date is defined as Day 1 and Study Day for each post-baseline assessment is attributed by Date of assessment – Date of first dose + 1. Study Day for assessment before first dose date will be calculated as Date of assessment – Date of first dose. Day 0 will not be used.

4.1.2.5 Visit windows and Unscheduled/Discontinuation visits

In principle, all the analysis will be performed based on nominal visit basis as reported in eCRF. Unscheduled/discontinuation visit will not be mapped to scheduled visit but will be used for Baseline and Endpoint/LOCF derivation and extreme values summary for laboratory values.

4.2 Analysis methods

4.2.1 Study population

4.2.1.1 Disposition

The disposition of subjects for the enrollment period and the double-blind treatment period (12 week, 24 weeks as well as 52 weeks) will be summarized.

The disposition summary of enrollment period will include all subjects enrolled (who signed informed consent).

The disposition summary of the treatment period will include all randomized subjects, and be presented by treatment group and total. This summary will include subjects completing and discontinuing the first 12-week, 24-week as well as 52 week treatment period with reasons for discontinuation.

4.2.1.2 Demographic and other baseline characteristics

Demographic and other baseline characteristics will be summarized by treatment group.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, min, max) will be presented. For categorical variables number and proportion of patients in each category will be presented.

Demographic and baseline characteristics will include but not limited to age, gender, body weight, height, BMI, concurrent use of statin, baseline TG, baseline LDL-C and other baseline values of selected lipid parameters as well as some co-morbidities.

4.2.1.3 Medical/surgical histories and current medical conditions

The number (percent) of subjects with medical history findings and current medical conditions will be summarized by treatment group.

4.2.2 Efficacy

4.2.2.1 Analysis of primary efficacy variable

The primary efficacy variable is the percent change in TG from baseline to week 12 Endpoint. The primary efficacy analysis for the percent change in TG will be based on analysis of covariance (ANCOVA) model, with fixed categorical effects of treatment, statin usage, as well as continuous fixed covariate of baseline TG value. For comparisons of each AZD0585

dose vs. Placebo pair-wise comparison, variance estimated from each pair will be employed. Primary analysis will be carried out for FAS.

The model will provide least-squares (LS) mean estimates, standard errors and 2-sided 95% confidence intervals (CIs) for mean change at Week 12 Endpoint within and between treatments. Unadjusted two sided P-values will be calculated based on the model. Confirmatory hypothesis testing will be based on Hochberg procedure as described in section 4.1.1.1. If a (two-sided) p-value for either dose is less than 0.05/2 = 0.025, superiority of the corresponding AZD0585 dose to Placebo will be claimed. If both p-values (for 2g and 4g dose groups) are less than 0.05, then superiority of both AZD0585 doses to placebo will be claimed.

Sensitivity analysis of primary efficacy variable

To assess the robustness of the primary efficacy analysis, and to compare the results with previous studies, the sensitivity analyses on the primary efficacy variable will be carried out using the following approaches.

Per Protocol analysis

Primary analysis by the same ANCOVA model for percent change in TG from baseline to week 12 Endpoint will be repeated for Per-Protocol Set.

Analysis based on log transformation

Change from baseline in log-transformed TG values at Week 12 Endpoint will be analyzed by ANCOVA model with fixed categorical effects of treatment, statin usage, as well as continuous fixed covariate of log-transformed baseline TG value. LSmeans and 95%CIs for each treatment and treatment difference will be back-transformed and presented as mean percent change from baseline and as relative treatment difference to Placebo in percent change. Nominal p-values will also be reported from the models. The detail of transforming quantity from analysis in log scale to percent change is provided in the table below:

Table 2 Transformation of quantities from log-transformed analysis

Quantities	Derivation
Adjusted mean percent change from baseline	100 × [exp(Adjusted mean change from baseline in natural logarithm) – 1]
Lower confidence limit for adjusted mean percent change from baseline	100 × [exp(lower confidence limit for adjusted mean change from baseline in natural logarithm) – 1]
Upper confidence limit for adjusted mean percent change from baseline	100 × [exp(upper confidence limit for adjusted mean change from baseline in natural logarithm) – 1]
Relative difference to Control in adjusted mean percent change from baseline.	100 × (exp(difference in adjusted mean change from baseline between AZD0585 treatment arm and Control in natural logarithm) – 1)

Quantities	Derivation
Lower confidence limit for relative difference to Control in adjusted mean percent change from baseline	100 × (exp(lower confidence limit for difference in adjusted mean change from baseline between AZD0585 treatment arm and Control in natural logarithm) – 1)
Upper confidence limit for relative difference to Control in adjusted mean percent change from baseline	100 × (exp(upper confidence limit for difference in adjusted mean change from baseline between AZD0585 treatment arm and Control in natural logarithm) – 1)

Nonparametric analysis

In order to address potential deviation from normality of percent change metric, treatment comparison on percent change of TG to Week 12 Endpoint will be conducted by two-sample Wilcoxon test. Treatment difference for location (median) shift will be presented with Hodges-Lehmann estimators and nonparametric 95%CIs.

Primary efficacy variable within subgroups

The primary efficacy variable of TG at Week 12 Endpoint will be descriptively summarized and analyzed similarly for the subgroups defined on the basis of the categorized variables listed in Table 3. Descriptive summary statistics would include, n, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, maximum.

Table 3 Subgroup analyses of primary efficacy variable

Group variable	Subgroups
Gender	Male, Female
Age	< 65 yrs >= 65 yrs
Body Mass Index	< 25 kg/m^2 >= 25 kg/m^2
Baseline triglyceride	< 300 mg/dL >= 300 mg/dL
Concurrent use of statin	Yes, No
Baseline LDL-C	< 140 mg/dL >= 140 mg/dL
Baseline HDL-C	< 40 mg/dL >= 40 mg/dL
Baseline non-HDL-C	< 170 mg/dL >= 170 mg/dL

Group variable	Subgroups
Baseline VLDL-C	< 60 mg/dL >= 60 mg/dL
Comorbidity – established CVD	Yes, No
Comorbidity – Hypertension	Yes, No
Comorbidity - Diabetes	Yes, No

4.2.2.2 Analysis of secondary efficacy variables

Fasting lipids (as defined in section 3.2.1)

The percent change from baseline of each fasting lipid parameter to the Week 12 Endpoint will be analyzed by ANCOVA model, with fixed categorical effects of treatment, statin usage, baseline TG strata (<300, >= 300 mg/dL) as well as continuous fixed covariate of corresponding baseline value. All the analyses will be carried out primarily for FAS and will be repeated for PPS.

The model will provide least-squares (LS) mean estimates, standard errors and 2-sided 95% confidence intervals for mean change at Week 12 Endpoint within and between treatments. Nominal two-sided p-values will also be displayed.

Other secondary efficacy parameters except for fasting lipids (as defined in section 3.2.2)

The percent change from baseline of each secondary efficacy parameter to Week 12 (LOCF) will be analyzed by ANCOVA model, with fixed categorical effects of treatment, statin usage, TG strata (<300, >= 300 mg/dL) as well as continuous fixed covariate of corresponding baseline value. All the analyses will be carried out for FAS only.

The model will provide least-squares (LS) mean estimates, standard errors and 2-sided 95% confidence intervals for mean percent change at Week 12 (LOCF) within and between treatments. Nominal two-sided p-values will also be displayed.

4.2.2.3 Analysis of exploratory efficacy variables

The time course of continuous efficacy variables will be presented using descriptive summary statistics by treatment and visit. For Week 12 Endpoint and Week 52 Endpoint, absolute change from baseline and percent change from baseline will also be presented. Descriptive summary statistics would include, n, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, maximum.

Descriptive summaries for selected secondary variables (including fasting lipids) will also be provided if deemed necessary based on the subgroup defined in Table 3.

4.2.3 Safety

For all safety evaluation, safety set will be used. In general, safety will be evaluated for the first 12-week treatment period as well as for 24-week or 52-week treatment period respectively at interim data base lock as well final data base lock.

4.2.3.1 Extent of exposure

Study medication

The extent of exposure to study medication is defined as last dose data – first dose date + 1.

The number and percent of subjects with an extent of exposure within pre-specified day ranges will be presented by treatment group. The categorization will be >=1 day, >= 4 weeks, >= 8 weeks, >= 12 weeks, >= 24 weeks, >= 36 weeks, >= 48 weeks and >= 52 weeks. The mean, standard deviation (SD), median and range of the number of days of exposure will also be presented.

Concomitant statin at baseline

Concurrent use of statin at baseline will be identified as those used at randomization day. Number of patients treated by statin at baseline will be summarized by treatment group, broken down by statin generic name.

General prior and concomitant medications

Prior medication will be defined as any medication taken before first dose of study drug. Concomitant medication will be defined as any medication taken on or after first dose of study medications. Medication which started before first dose of study drug and continued during study treatment will be counted in both prior medication and concomitant medication.

Prior and concomitant medications will be summarized using the Safety Set by drug class and (generic) drug name. A summary table by drug class and generic drug name will be generated for each of the following:

- all prior medication (excluding lipid lowering medication)
- all concomitant medication (excluding lipid lowering medication) taken during the first 12-week treatment period
- all concomitant medication (excluding lipid lowering medications) taken during the first 24-week treatment period
- all concomitant medication (excluding lipid lowering medications) taken during the whole treatment period (up to 52 weeks)
- prior lipid lowering medication
- concomitant lipid lowering medication during first 12-week treatment period

- concomitant lipid lowering medication during first 24-week treatment period
- concomitant lipid lowering medication during the whole treatment period (up to 52 weeks)

The WHO dictionary is used to code the non-study medication.

4.2.3.2 Adverse events

Treatment-emergent adverse events (TEAEs, i.e. adverse events with onset on or after first dose of study drug) will be summarized for safety evaluation. Adverse events occurring before start of study drug will only be listed.

Adverse events (AEs) will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs will use the version of MedDRA that is current at the time of database lock.

All adverse events

All AEs with onset during the first 12-week (+2 days) treatment period, 24-week (+7 days) treatment period and with onset during the whole study treatment period will be summarized. The following items will be summarized by system organ class, preferred term and treatment group.

- Any AEs
- Deaths
- Serious AEs (SAEs)
- AEs leading to study drug discontinuation (DAEs)
- AEs by maximum intensity
- AEs related to study drug

4.2.3.3 Safety Laboratory evaluation

Hematology and Clinical Chemistry

For quantitative variables, descriptive summary statistics (for value at visit and change from baseline) will be provided by visit and treatment group.

Shift tables in categories of low, normal, and high (based on normal range of central laboratory) will be summarized by treatment group using the baseline (Week 0) values and the highest and lowest values obtained during the first 12 weeks, 24 weeks as well as during the whole 52-week study treatment period. Percentages will be based on the number of subjects

within each treatment group with each baseline status. In this summary, unscheduled measurement will also be counted in.

Liver enzyme abnormalities

For liver safety, additional summary of proportion of subjects with elevated liver enzymes will be provided by treatment group. Liver enzyme abnormalities are defined as the Table 4.

Table 4 Liver enzyme abnormalities

Parameter	Criteria
ALT	>3, >5, >10, >20xULN
AST	>3, >5, >10, >20xULN
AT (ALT or AST)	>3, >5, >10, >20xULN
TBL	>1.5, >2xULN
ALP	>1.5, >3xULN
AT & TBL	AT > 3xULN & TBL > 1.5xULN, AT > 3xULN & TBL > 2 xULN
AT & TBL & ALP	AT > 3xULN & TBL > 2xULN & ALP < 2xULN

ALT = alanine aminotransferase, AST = aspartate aminotransferase, AT = alanine or aspartate aminotransferase, TBL = total bilirubin, ULN = upper limits of normal

Urinalysis

For qualitative variables (measured by dipstick test), shift table from baseline to post-baseline will be produced by visit and treatment group.

4.2.3.4 Vital signs

Descriptive summary statistics (for value at visit and change from baseline) will be provided by visit and treatment group.

4.2.3.5 Physical examination

All results of physical examination will be listed for each patient.

4.2.3.6 Electrocardiograms

For all continuous measurements (HR, RR, PR, QRS and QT) as well as QTcF (derived by QTcF and RR) will be summarized descriptive statistics by treatment group and visit.

QTcF will be derived as: $QTcF = QT / \sqrt[3]{RR}$

Abnormal prolongation of QTcF will be summarized by treatment group based on criteria specified in the Table 5. The extreme (highest) value for a patient during treatment will be used this summary.

Table 5 Categorical evaluation of QTcF

Parameter	Criterion
QTcF	>450 msec
	>480 msec
	>500 msec
Change from baseline in QTcF	>30 msec
	>60 msec

Shift table for the investigators assessment on abnormality will also be created by visit and treatment group.

5. INTERIM ANALYSES

An interim analysis will include all patients' data available until data cut-off, including primary/secondary analysis at Week 12 Endpoint for efficacy as well as safety evaluation based on 24-week or longer exposure to study drug. Sponsor will be unblinded at the time of interim analysis but investigators, patients and site-staff will not be informed of assigned treatment in order to maintain integrity as much as possible. Data cut off date is defined as a day when 24 weeks have passed after Last Subject In (LSI). This interim analysis will be documented as an interim clinical study report.

6. CHANGES OF ANALYSIS FROM PROTOCOL

While in the protocol, sensitivity analysis based on log-transformed data was planned to model including log-transformed post-baseline TG value as a response variable, it was changed to model change from baseline in log-transformed TG value in order to facilitate easier transformation of quantity related to the percent change from baseline in each arm. In terms of statistical treatment comparison, these two approaches are equivalent.

7. REFERENCES (NOT APPLICABLE)

8. APPENDIX (NOT APPLICABLE)