STATISTICAL ANALYSIS PLAN

A Randomized Double-Blind Placebo Controlled Study Characterizing The Effects of PCSK9 Inhibition On Arterial Wall inflammation in Patients With Elevated Lp(a) (ANITSCHKOW)

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AHA	American Heart Association
AI	Autoinjector
ALT	Alanine aminotransferase
ANCOVA	analysis of covariance
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
CHD	Coronary Heart Disease
CK	Creatine phosphokinase
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DRE	Disease-related event
eCRF	Electronic Case Report Form
EOIP	End of Investigational Product
EOS	End of study (for individual subject)
FAS	Full analysis set
FDG	Fluorodeoxyglucose
FDG-PET/CT	Fluorodeoxyglucose-positron emission tomography/computed tomography
HDL-C	High-density lipoprotein cholesterol
hsCRP	High sensitivity C-reactive protein
IP	Investigational product
IPD	Important protocol deviation
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
Lp(a)	Lipoprotein(a)
MDS	Most diseased segment
MedDRA	Medical dictionary for regulatory activities
NCEP	National Cholesterol Education Program
OxPL	Oxidized phospholipids

Abbreviation or Term	Definition/Explanation
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
QM	Monthly (Every 4 weeks)
QD	Once a day
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SCIPD	Dose date of SC investigational product
SD	Standard deviation
TBR	Target-To-Background Ratio
TEAE	Treatment-Emergent Adverse Event
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment 3 for evolocumab Study 20130293 dated 8 February 2017. The scope of this plan includes the final analysis that are planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 Primary

To evaluate the effect of evolocumab on arterial wall inflammation, as measured by percent change from baseline in target-to-background ratio (TBR) of an index vessel by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) at week 16 in subjects with baseline lipoprotein (a) [Lp(a)] ≥ 50 mg/dL and low density lipoprotein-cholesterol (LDL-C) ≥ 100 mg/dL.

2.2 Secondary

- To evaluate the effect of evolocumab on Lp(a), as measured by percent change from baseline at week 16 in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL
- To evaluate the effect of evolocumab on LDL-C, as measured by percent change from baseline at week 16 in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL
- To evaluate the effect of evolocumab on Apolipoprotein B (ApoB), as measured by percent change from baseline at week 16 in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL

2.3 Safety

To evaluate the safety of evolocumab in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL

2.4 Exploratory

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3. Study Overview

3.1 Study Design

This is a phase 3b, multi-center, double-blind, randomized, placebo-controlled study evaluating the effect of evolocumab on arterial wall inflammation as measured by FDG PET/CT following 16 weeks of treatment in subjects with elevated levels of Lp(a). Eligible subjects will have hyperlipidemia with Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL. In addition, the subjects must have TBR max > 1.6 on FDG PET/CT in order to qualify for enrollment. If subjects are on statin or other lipid-lowering therapy (not required to participate in this study), they must be on a stable dose for at least 8 weeks prior to screening and during the entire time of screening and throughout the study.

The study will include 2 screening visits (screen 1 and screen 2) during the screening period, which will be a maximum total of 56 days. Subjects will be randomized 1:1 into 2 treatment groups: evolocumab 420 mg QM SC or placebo QM SC. Randomization will be stratified for balance by baseline background statin therapy (on statin vs not on statin) and by screening Lp(a) (< 175 mg/dL or ≥ 175 mg/dL). The treatment period will be 12 weeks in duration with study visits every 4 weeks. At the end of study (EOS) visit at week 16, FDG PET/CT will be conducted.

3.2 Sample Size

At present, PCSK9 inhibitors have not been evaluated for their ability to lower arterial wall inflammation. Therefore, we have used an efficacy study with atorvastatin aimed to lower LDL-C and arterial wall inflammation for our sample size estimation (Tawakol et al, 2013). The planned sample size is 120 subjects (60 in evolocumab and 60 in control). Based on Tawakol et al, 2013, we make an assumption that each 10% reduction in LDL-C results in an approximate reduction of 2.4% in MDS TBR. Further assume that 70% of the subjects will be on a statin and 30% will not be on a statin. From the results of the phase 3 evolocumab studies, a treatment effect of evolocumab QM over placebo in the percentage reduction in LDL-C at week 16 is assumed to be 55% for subjects who are not on a statin and 60% for patients who are on a statin. From the assumption that 10% of LDL-C reduction induces an approximate 2.4% of TBR reduction, we expect to observe a combined reduction of 14.0% in MDS TBR at week 16 in the evolocumab group compared to the control group. A combined standard deviation of 20.0% for the percentage change from baseline to week 16 is assumed for MDS TBR. After accounting for a dropout rate of 25%, the power is greater

than 90% for testing superiority of evolocumab over placebo on the percentage change in MDS TBR at week 16.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoints

Percentage change from baseline in TBR within the MDS of the index vessel (right carotid, left carotid, or thoracic aorta) by FDG-PET/CT at week 16

4.1.2 Secondary Endpoints

- Percentage change in Lp(a) from baseline at week 16
- Percentage change in LDL-C from baseline at week 16
- Percentage change in ApoB from baseline at week 16

4.1.3 Safety Endpoints

Subject incidence of treatment-emergent adverse events compared to placebo for the duration of the study

4.1.4 Exploratory Endpoints

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[redacted]

4.2 Planned Covariates

No covariate is planned.

5. Hypotheses and/or Estimations

The primary statistical hypothesis is as follows:

The null hypothesis is that there is no difference in the mean percent change from baseline at week 16 in TBR within the MDS of the index vessel between evolocumab and placebo, and the alternative hypothesis is that a mean difference does exist.

6. Definitions

6.1 Study Time Points

Enrollment Date

Enrollment Date is the same as Randomization Date.

Randomization Date

The date a subject is randomized in the interactive voice response system (IVRS)/interactive web response system (IWRS) as recorded on the eCRF.

First Dose Date of Investigational Product

For each subject, the First Dose Date of Investigational Product (IP) is defined as the first administration date of IP (evolocumab or placebo) as recorded on the IP administration eCRF.

Study Day 1

For each subject, Study Day 1 is defined as the first day that protocol-specified investigational product is administered to the subject. If a subject is randomized but never received IP, Study Day 1 is defined as the Randomization Date.

Study Day

For each subject, and for a given date of interest, Study Day is defined as the number of days since Study Day 1:

Study Day = (date of interest – Study Day 1 date) + 1.

If the date of interest is prior to the Study Day 1:

Study Day = (date of interest – Study Day 1 date), so that the day prior to Study Day 1 is study day -1.

Last Dose Date of Investigational Product

For each subject, the Last Dose Date of Investigational Product is defined as the date of the last administration of IP (evolocumab or placebo).

End of Study (EOS) Date

For each subject, the End of Study Date is the date recorded on the End of Study eCRF.

Study End Date

The Study End Date is the last EOS date of all randomized subjects.

6.2 Demographics and Baseline Related Definitions

Age

Age will be calculated or collected as the subject's age in years at enrollment as recorded on the eCRF.

Baseline Lipid and Lipid-related Parameters

Baseline values for fasting lipids (total cholesterol, HDL-C, LDL-C, VLDL-C and triglycerides), ApoA1, ApoB, CRP, Lp(a) and their derived parameters (eg, ratio between them) are defined as the mean of the two most recent non-missing fasting concentrations measured through central lab prior to or on Study Day 1. If for any reason only 1 value is available, then that value will be used as the baseline.

Other Baseline Values

For HbA1c and all other variables, the baseline value is defined as the last non-missing value collected prior to or on Study Day 1.

Change (absolute change) from Baseline

The arithmetic difference between a post-baseline value and baseline for a given time point:

Change (absolute change) from baseline = (post-baseline value – baseline value)

Percent Change from Baseline

The percent change from baseline for a given variable at a given time point is defined as: 100% x [(value at given time point – baseline value) / baseline value]

Baseline CHD Risk Factors

A subject will be categorized as having 2 or more CHD Risk Factors (Y/N) from the list of the modified NCEP ATP III risk factors:

- current cigarette smoking
- hypertension
- type II diabetes mellitus
- family history of premature CHD as recorded on the eCRF
- low HDL-C defined as baseline HDL-C < 40 mg/dL in men and < 50 mg/dL in women.

Baseline National Cholesterol Education Program (NCEP) Risk Categories

Risk Factor	Defining Level
High Risk: CHD or CHD Risk Equivalent	Coronary Artery Disease OR Cerebrovascular or Peripheral Vascular Disease OR Type 2 Diabetes Mellitus OR 2 or more Risk Factors (see below) AND FRS > 20% (see Appendix A for FRS calculation)
Moderately High Risk	NOT High Risk AND 2 or more Risk Factors AND FRS ≥ 10% AND ≤ 20%
Moderate Risk	NOT High Risk AND 2 or more Risk Factors AND FRS < 10%
Lower Risk	NOT High Risk AND 0 to 1 Risk Factor

Risk Factors for NCEP Risk Categories:

Risk factors are: current cigarette smoking, hypertension or (baseline SBP ≥ 140 or DBP ≥ 90 mmHg), family history of premature CHD as recorded in the eCRF form, low HDL-C cholesterol defined as baseline HDL-C < 40 mg/dL, age ≥ 45 years in men or ≥ 55 years in women.

Risk Classification According to ESC/EAS Guidelines

The Systematic Coronary Risk Estimation (SCORE) system estimates the 10 year risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death (ESC/EAS 2011). The SCORE risk estimates will be computed from the high and low risk region tables based on sex and baseline smoking status, systolic blood pressure, total cholesterol and age. Risk classification of very high, high, moderate and low risk will be according to the ESC/EAS guidelines.

6.3 Other Study Related Definitions

Analytical Study Week Assignments

Analytical windows will be used to assign parameter measurements to study weeks. The algorithm is provided in Appendix B.

Actual Treatment Group

A subject's actual treatment group is the randomized treatment group, unless the subject receives treatment throughout the study that is different than the randomized treatment group assignment, in which case the actual treatment group is the treatment received.

Investigational Product (IP)

IP includes SC evolocumab 420 mg QM and its corresponding SC placebo.

IP Exposure Period in Months

IP Exposure in Months = [min (Last Dose Date of IP + 28 days, EOS Date) - Study Day 1 +1] / 365.25 * 12.

Study Exposure Period in Months

For each randomized subject, Study Exposure in Months = (EOS date – Enrollment Date + 1) / 365.25 * 12.

Treatment Emergent Adverse Event (TEAE)

Treatment emergent adverse events are adverse events occurring from the first dose of IP date up to and including 30 days after the last dose of IP date or the EOS date whichever occurs first. Adverse events will be considered as treatment emergent if answer to the question "Did event start before first dose of investigational product?" on the eCRF is not "Yes".

Treatment-Emergent Disease-Related event

Treatment emergent disease-related events are events categorized as Disease-related Events (DREs) starting on or after first dose of investigational product and up to and including the end of study.

LDL-C Reflexive Approach

For all analyses related to LDL-C, unless specified otherwise, a LDL-C reflexive approach will be used. When calculated LDL-C is less than 40 mg/dL or triglycerides > 400 mg/dL, the UC LDL-C value from the same blood sample will be used instead, if available.

7. Analysis Subsets

7.1 Full Analysis Set

The full analysis set (FAS) includes all randomized subjects who receive at least one dose of IP. This analysis set will be used in both efficacy and safety analyses. In efficacy

analysis, subjects will be analyzed according to their randomized treatment group assignment. For safety analysis, subjects will be analyzed according to their randomized treatment group assignment except for the following case: if a subject receives a treatment that is different than the randomized treatment assignment throughout the study, then this subject will be analyzed by the treatment received.

7.2 Subgroup Analyses

Subgroup by

- Baseline background statin therapy: on statin vs not on statin
- Screening Lp(a): < 175 nmol/L vs ≥ 175 nmol/L
- Baseline Lp(a): < Median vs ≥ Median

8. Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

All data collected in the eCRF will be extracted from RAVE. Protocol deviations will be transferred from eClinical. Final PK data for all randomized subjects will be transferred from statistical programming to Amgen's PKDM group. Unblinded subject and box ID randomization lists will be provided by Amgen's randomization group and the IVRS when the study stops. Details on data transfer will be provided in the Data Transfer Plan.

9.3 Handling of Missing and Incomplete Data

9.3.1 Patterns of Missing Data

Subjects may be missing specific data points for various reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of a data point or an endpoint at a particular point in time. In the Data Quality Review (DQR) process, queries will be made to the sites to distinguish true missing values from other unknown values (eg, due to measurement or sample

processing error). All attempts will be made to capture missing or partial data for this trial prior to the database lock.

The frequency and pattern of missing data for efficacy endpoints will be assessed through descriptive summaries of the measurements over time.

9.3.2 Handling of Incomplete Dates

Adverse event or concomitant medication with completely or partially missing dates will be queried. If after the query is resolved, the date is still incomplete with year only or year and month only, the start date will be imputed as described in Table 1 below:

Table 1. Imputation Rules for Incomplete Dates

	Missing	Imputation	Exception
Start date (AE and concomitant medication)	Day	1	Default to Study Day 1 if an event starts the same year and month as Study Day 1
	Day/Month	1-Jan	Default to Study Day 1 if an event started the same year as Day 1

9.4 Detection of Bias

This study has been designed to minimize potential bias by the use of randomization of subjects into treatment groups and the use of blinding. Other factors that may bias the results of the study include:

- major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- subject level unblinding before primary database lock and formal unblinding

Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the Clinical Study Report (CSR).

Any unblinding of individual subjects prior to formal unblinding of the study will be documented in the CSR. The impact of such unblinding on the results observed will be assessed. Data from subjects whose treatment assignments are unblinded prior to formal unblinding will be listed. The timing and reason for unblinding will be included in these listings.

The units for the stratification factor based on Lp(a) (final screening Lp(a) < 175 mg/dL vs ≥ 175 mg/dL) was not stated correctly in the protocol, which led to the an incorrect stratification factor being used in the randomization. This may potentially bias the results as there may be an imbalance between treatment groups in the intended stratum (final

screening Lp(a) <175 nmol/L vs ≥ 175 nmol/L). This potential imbalance will be explored in sensitivity analyses by adding the intended Lp(a) stratum as a baseline covariate and as a subgroup. Subgroup analysis by median baseline Lp(a) will also be performed.

Additional sensitivity analyses may be included to assess the impact of potential biases on the primary endpoint. If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, then the sources of the potential biases and results of the sensitivity analyses will be documented in the CSR.

9.5 Outliers

Various methods, including univariate summaries, histograms, scatter plots, box plots, and line graphs, may be used to identify outliers in key safety and efficacy variables. Extreme data points will be identified during the blinded review of the data prior to database lock. Such data points will be reviewed with clinical data management to ensure accuracy. The primary analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

9.6 Distributional Characteristics

Distributional assumptions for the primary and secondary co-endpoints will be assessed. If the assumptions are not met, then alternative methods will be utilized. The use of alternative methods will be fully justified in the CSR.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.2 or later.

10. Statistical Methods of Analysis

10.1 General Principles

Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized by treatment group.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, the 1st (Q1) and 3rd (Q3) quartiles,

minimum, and maximum. For categorical variables, the frequency and percentage will be given. No adjustments for multiplicity will be applied.

The final analysis will be conducted when all subjects have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned, processed and the database will be locked; the study will also be unblinded. Efficacy and safety analyses will be performed on the FAS.

Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by randomized treatment group for evolocumab and placebo. The superiority of evolocumab to placebo will be assessed for all efficacy endpoints. The primary analysis will include testing for the primary and secondary endpoints. Lp(a) data from Medpace Reference Laboratories (MRL) will be used in the primary analysis.

Methods of handling missing data for efficacy endpoints will be described throughout this section. Missing data will not be imputed for safety endpoints.

10.2 Subject Accountability

The number of subjects screened, randomized to IP, receiving IP, and completing the study will be summarized. Key study dates for the first subject enrolled, last subject enrolled and last subject's end of study will be presented. The number and percent of subjects randomized will be tabulated by the stratification factors.

Study discontinuation and IP discontinuation will be tabulated separately by reasons for discontinuation.

The number of subjects included in and excluded from each analysis set and reason for exclusion will also be summarized.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study.

Eligibility deviations are defined in the protocol.

10.4 Demographic and Baseline Characteristics

Demographic (ie, age, geriatric age group [< 65, >= 65 and >= 75], sex, race, ethnicity) and baseline disease characteristics (cardiovascular medical history, laboratory parameters, and lipid-regulating medication) will be summarized by treatment group and

overall using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race. Difference in stratum assignment between IVRS/IWRS stratum and data-derived stratum will be tabulated.

10.5 Efficacy Analyses

The following table summarizes the key efficacy analyses that will be conducted for the primary analysis.

Endpoint	Primary Analysis Method	Sensitivity Analysis
Primary Endpoint		
• Percentage change from baseline in MDS TBR at week 16	• Multivariate regression model on FAS with dependent variables percent change from baseline in MDS TBR, percent change from baseline in Lp(a), baseline MDS TBR, and baseline Lp(a).	• Primary analysis model repeated on FAS excluding FDG-PET/CT observations made after an on-study cardiovascular event • Covariate and subgroup analyses
Secondary Endpoints		
• Percentage change in Lp(a) from baseline at week 16 • Percentage change in LDL-C from baseline at week 16 • Percentage change in ApoB from baseline at week 16	• Repeated measures model on the FAS including terms for treatment group, baseline statin use stratification factor, scheduled visit, and the interaction of treatment with scheduled visit	• Multiple imputation for subjects with missing Lp(a) data
Exploratory Endpoints		
• CCI [redacted]	• Summary statistics at week 16	

10.5.1 Analyses of Primary Efficacy Endpoint

10.5.1.1 Primary Analysis of Primary Endpoint

The primary endpoint is the percentage change from baseline in MDS TBR at week 16. In order to estimate the difference in mean percentage change from baseline in MDS

TBR and to handle missing data for the primary endpoint, a multivariate regression model will be used. The response variables are percent change from baseline in MDS TBR at week 16, baseline MDS TBR, percent change from baseline in Lp(a) at weeks 8 and 16, and baseline Lp(a). Each response follows its own regression model:[1]

- Percent change in MDS TBR will be regressed on treatment group and the stratification factor (on a statin, not on a statin);
- Baseline MDS TBR will be regressed on the stratification factor (on a statin, not on a statin);
- Percentage change in Lp(a) will be regressed on the treatment group, stratification factor (on a statin, not on a statin), visit, and treatment group by visit;
- Baseline Lp(a) will be regressed on the stratification factor (on a statin, not on a statin).

The variance-covariance matrix of the error terms from the response variables in the multivariate regression will be estimated. This analysis will use the FAS.

10.5.1.2 Sensitivity Analysis of Primary Endpoint

- The model specified in Section 10.5.1.1 will be repeated[1]
  - by adding covariate screening Lp(a) < 175 nmol/L and ≥ 175 nmol/L,
  - by subgroups specified in Section 7.2.
- FDG-PET/CT observations made after an on-study cardiovascular event will be included in the primary analysis. A sensitivity analysis excluding these observations will be conducted.

For subgroup and covariate analyses, the data-derived stratification factor will be used. Difference in stratum assignment between IXRS/IWRS stratum and data-derived stratum will be tabulated.

10.5.2 Analyses of Secondary Efficacy Endpoints

To assess the mean percent change from baseline in the secondary endpoints of Lp(a), LDL-C, and ApoB, a repeated measures linear effects mixed model will be used on the FAS to compare the efficacy of evolocumab with placebo. The model will include the treatment group, stratification factor (on a statin, not on a statin), visit, and the interaction of treatment group and visit.

[1] See section 11.

To evaluate the impact of missing Lp(a),

- A sensitivity analysis under the assumption that subjects that discontinued IP and have missing endpoint data have a mean zero percent change from baseline will be conducted using multiple imputation.
- The mixed model will be repeated using FAS with missing values imputed for subjects who discontinued IP. Missing values will be imputed using non-missing data from subjects who discontinued IP within the same treatment group, provided that there is a sufficient number of subjects in each treatment group who discontinue IP but have non-missing endpoint data.

10.5.3 Analyses of Exploratory Endpoints

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[redacted]

10.6 Safety Analyses

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later will be used to code all events categorized as adverse events (AEs) or disease related events to a system organ class and a preferred term. Severity of AEs will be graded using the CTCAE (Appendix C) and recorded on the eCRF. All adverse event tables will be summarized by actual treatment group.

Subject incidence of AEs will be summarized for all treatment-emergent AEs (TEAEs), serious TEAEs, TEAEs leading to withdrawal of investigational product, and fatal TEAEs.

Subject incidence of all TEAEs, serious AEs, AEs leading to withdrawal from investigational product will be tabulated by system organ class and preferred term in descending order of frequency.

Summaries of all TEAEs and serious TEAEs occurring in at least 1% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Subject incidence of device-related TEAEs will be tabulated by preferred term in descending order of frequency.

Subject incidence of treatment-emergent disease-related AEs (DREs) and treatment-emergent fatal DREs will be summarized by system organ class and preferred term in decending order of frequency.

10.6.2 Laboratory Test Results

Descriptive statistics will be provided for actual values and changes from baseline in select laboratory parameters at each protocol-specified scheduled visit. Laboratory analytes are prived in the Protocol section 7.5.

10.6.3 Vital Signs

Systolic and diastolic blood pressure and heart rate will be summarized for each treatment group using descriptive statistics at baseline visit.

10.6.4 Physical Measurements

Physical measurements will be summarized for each treatment group using descriptive statistics at baseline visit.

10.6.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group.

Exposure definitions are provided in Section 6.3.

10.6.6 Exposure to Concomitant Medication

The number and proportion of subjects receiving the medications of interest (MOI) will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary.

11. Changes From Protocol-specified Analyses

An error in the protocol was discovered regarding the units for the stratification based on screening Lp(a), where 175 mg/dL was used instead of the correct 175 nmol/L (protocol section 3.1). Therefore, the planned analyses in the SAP was updated prior to study closure and unblinding to the following: the primary analysis will stratify by baseline statin use only. The intended Lp(a) stratification factor (final screening Lp(a) < 175 nmol/L and ≥ 175 nmol/L) will be added to the primary analysis model as a covariate in a sensitivity analysis and be used in the subgroup analysis, and an additional subgroup analysis by baseline median Lp(a) will be performed. 175 nmol/L is equivalent to 70 mg/dL.

12. Literature Citations / References

Tawakol A, Fayad ZA, Mogg R, et al. Intensification of Statin Therapy Results in a Rapid Reduction in Atherosclerotic Inflammation: Results of A Multi-Center FDG-PET/CT Feasibility Study. *J Am Coll Cardiol.* 2013; 62:909-917.

Wilson PWF et al. Prediction of Coronary Heart Disease Using Risk Factor Categories. *Circulation.* 1998; 97:1837-1847.

13. Appendices

Appendix A. Framingham Risk Score (FRS)

Method to calculate the Framingham Risk Score (FRS):

The β coefficients given in the two tables below are used to compute a linear function. The latter is corrected for the averages of the participants' risk factors (mean) from the Framingham study, and the subsequent result is exponentiated and used to calculate a 10-year probability of HCHD after insertion into a survival function (Wilson et al, 1998).

The calculation is different for men and women and use the following coefficients β_i, where *i* represents each of the independent variables. The values below are from the Framingham heart study (http://www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/hard-10-year-risk.php).

t_chol = total cholesterol, hdl = HDL-C, sbp = systolic blood pressure, trt_htn = treatment for hypertension (if sbp > 120), smoker = current smoker

Men		
Independent variable	Coefficient βi	mean
ln(age)	52.00961	3.8926095
ln(t_chol)	20.014077	5.3441475
ln(hdl)	-0.905964	3.7731132
ln(sbp)	1.305784	4.8618212
trt_htn (spb>120)	0.241549	0.1180474
smoker	12.096316	0.335602
ln(age)* ln(t_chol)	-4.605038	20.8111562
ln(age)*smoker[1]	-2.84367	1.2890301
ln(age)*ln(age)	-2.93323	15.2144965
[1] if age>70 then ln(70)*smoker		

Women		
Independent variable	Coefficient βi	mean
ln(age)	31.764001	3.9213204
ln(t_chol)	22.465206	5.3628984
ln(hdl)	-1.187731	4.0146369
ln(sbp)	2.552905	4.8376494
trt_htn (spb>120)	0.420251	0.142802
smoker	13.07543	0.3236202
ln(age)* ln(t_chol)	-5.060998	21.0557746
ln(age)*smoker[2]	-2.996945	1.2519882
[2] if age>78 then ln(78)*smoker		

The steps to determine the FRS is the same for men and women.

<u>Men</u>

For each subject:

1. Calculate $L_{men} = \beta_{ln(age)}$*ln(age) + $\beta_{ln(t\_chol)}$*ln(t_chol) + $\beta_{ln(hdl)}$ *ln(hdl) + $\beta_{ln(sbp)}$*ln(sbp) + β_{trt_htn}*(if trt_htn) + β_{smoker}*(if smoker) + $\beta_{ln(age)*ln(t\_chol)}$*ln(age)*ln(t_chol) + $\beta_{ln(age)*smoker}$*ln(age)*(if smoker) + $\beta_{ln(age)*ln(age)}$*ln(age)*ln(age)
2. Calculate $A_{men} = L_{men}$ - 172.300168 (note: the value of 172.300168 was derived based on the mean columns in above table)
3. Calculate $B_{men} = \exp(A_{men})$
4. Calculate $P_{men} = 1 - 0.9402\text{^}B_{men}$
5. $FRS_{men} = P_{men}$*100 (rounded to nearest integer)

Women

For each subject:

1 Calculate $L_{women} = \beta_{ln(age)}*ln(age) + \beta_{ln(t\_chol)}*ln(t\_chol) + \beta_{ln(hdl)}*ln(hdl) + \beta_{ln(sbp)}*ln(sbp) + \beta_{trt\_htn}*(\text{if trt\_htn}) + \beta_{smoker}*(\text{if smoker}) + \beta_{ln(age)*ln(t\_chol)}*ln(age)*ln(t\_chol) + \beta_{ln(age)*smoker}*ln(age)*(\text{if smoker})$

2 Calculate $A_{women} = L_{women} - 146.5933061$ (note: the value of 146.5933061 was derived based on the mean columns in above table)

3 Calculate $B_{women} = \exp(A_{women})$

4 Calculate $P_{women} = 1 - 0.98767^{B_{women}}$

5 $FRS_{women} = P_{women}*100$ (rounded to nearest integer)

Notes

- For men, if subject is > age 70, then use ln(70)*smoker
- For women, if subject is > age 78, then use ln(78)*smoker
- For dichotomous variables trt_htn and smoker use 1/0 to represent yes/no respectively
    - If a subject has sbp ≤ 120 mmHg, then trt_htn is no

Calculated scores should match the interactive calculator

http://cvdrisk.nhlbi.nih.gov/calculator.asp

Appendix B. Technical Analytical Study Week Assignments

Selected endpoints will be summarized by scheduled study visits in descriptive analyses.

Since the actual visits may not exactly coincide with their scheduled visit day, the actual visit day is mapped to the study visit generally by non-overlapping consecutive intervals covering the entire time continuum. The mapping intervals for all distinct schedules are summarized in the following tables.

Scheduled Visit Week	Week 4	Week 8	Week 12	Week 16
Scheduled Visit Day	29	57	85	113
Fasting Lipids, ApoA1, ApoB, Lp(a)		(1, 84]		(84, 119]
FDG-PET/CT				>1
hsCRP				>1

Handling multiple records assigned to an analytical study week:

If there is more than one record in a study week interval, the analytical record for that specific study week will be defined as the record closest to the scheduled visit day of that specific study week (7 x study week + 1). If two records are equidistant from the scheduled day, then the earlier record will be chosen. If there are multiple records on the same day, the last record will be used.

Appendix C. Reference Values/Toxicity Grades

Refer to the NCI CTCAE Version 4.0 for AE grading and information. The CTCAE is available at the following

link:http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.