STATISTICAL ANALYSIS PLAN

A Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy in Patients With Clinically Evident Cardiovascular Disease

Protocol Number: **20110118**

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
ADD	Adjudicated Death Date
AE	Adverse event
AHA	America Heart Association
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BMI	Body mass index
CEC	Clinical Events Committee
CHD	Coronary Heart Disease
CI	Confidence interval
CK	Creatine phosphokinase
CMH	Cochran Mantel-Haenszel
CV	Cardiovascular
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CSR	Clinical study report
CTCAE	NCI Common Terminology Treatment Collaboration
DBP	Diastolic blood pressure
EDDVP	End Date of EOS Visit Period
DMC	Data Monitoring Committee
DQR	Data Quality Review
EC	Executive Committee
ECG	Electrocardiogram
EOI	Event of Interest
EOIP	End of Investigational Product
EOS	End of study
EOSVS	End of study vital status
FAS	Full analysis set
HDL-C	High density lipoprotein cholesterol
HR	Hazard Ratio

Abbreviation or Term	Definition/Explanation
hsCRP	High sensitivity C-reactive protein
IBG	Independent biostatistical group
IP	Investigational product
IPD	Important protocol deviation
ITT	Intent to treat
IVRS	Interactive voice response system
K-M	Kaplan-Meier
LPEPD	Last non-fatal potential endpoint collection date
LCSSD	Last confirmed survival status date
LDL-C	Low density lipoprotein cholesterol
LMC	Lipid monitoring committee
Lp(a)	Lipoprotein(a)
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
PAD	Peripheral arterial disease
PCSK9	Proprotein convertase subtilisin/kexin type9
PK	Pharmacokinetic
PKDM	Pharmacokinetics and drug metabolism
PPAS	Per Protocol Analysis Set
Q2W	Every 2 weeks
QM	Monthly (Every 4 weeks)
QD	Once a day
SAE	Serious adverse event
SAP	Statistical analysis plan
SDEVP	Start date of the EOS visit period
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
TEAE	Treatment emergent adverse event
TIA	Transient ischemic attack
UC	Ultracentrifugation
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 6 for evolocumab Study 20110118 . The scope of this plan includes the final analysis that is planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 Primary Objective

To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurs first, in subjects with clinically evident cardiovascular disease

2.2 Secondary Objectives

Secondary objectives are to evaluate the effect of treatment with evolocumab, compared with placebo, in subjects with clinically evident cardiovascular disease on the risk for:

- cardiovascular death, myocardial infarction, or stroke
- cardiovascular death
- death by any cause
- myocardial infarction
- stroke
- coronary revascularization
- cardiovascular death or hospital admissions for worsening heart failure
- fatal or non-fatal ischemic stroke or transient ischemic attack (TIA)

2.3 Exploratory Objectives

Exploratory objectives are:

- To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for coronary death in subjects with clinically evident cardiovascular disease
- To evaluate the effect of treatment with evolocumab, compared with placebo, on the total number of events from the components of the primary endpoint (myocardial infarction, hospitalization for unstable angina, stroke, coronary revascularization, and cardiovascular death), in subjects with clinically evident cardiovascular disease
- To evaluate the effect of treatment with evolocumab, compared with placebo, on proprotein convertase subtilisin/kexin type 9 (PCSK9) levels, on hemoglobin A1c (HbA1c), on percent of subjects attaining an LDL-C treatment goal of < 70 mg/dL (1.8 mmol/L), and on change and percent change from baseline of LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio,

triglycerides, VLDL-C, HDL-C, ApoA1, Lp(a), and high sensitivity C-reactive protein (hsCRP) in subjects with clinically evident cardiovascular disease

- To investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of evolocumab
- In subjects consenting to the optional pharmacogenetics analysis, to investigate potential correlations of study data including the subject response to evolocumab with genetic variation in markers of PCSK9 signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism, inflammation, and plaque stability.

2.4 Safety Objective

To evaluate the safety and tolerability of evolocumab, compared with placebo, in subjects with clinically evident cardiovascular disease

3. Study Overview

3.1 Study Design

This is a phase 3, multicenter, double-blind, randomized, placebo controlled, parallel group, cardiovascular outcomes study for evolocumab in subjects with clinically evident cardiovascular disease as evidenced by a history of myocardial infarction, non-hemorrhagic stroke, or symptomatic peripheral arterial disease (PAD). At randomization, subjects must be receiving stable, optimized lipid lowering background therapy per Appendix E of the protocol, that is expected to be unchanged for the duration of study participation (up to approximately 5 years). Subjects must receive at least an effective statin dose, ie, at least atorvastatin 20 mg daily or equivalent. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C $>$ 100 mg/dL and not receiving highly effective statin therapy (atorvastatin $\geq$ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, subject refused, dose not tolerated, dose not available in that country, other significant concern).

Eligible subjects will be randomized with an allocation ratio of 1:1 to either receive evolocumab or placebo. Randomization will be stratified by the final screening LDL-C level ($<$ 85 mg/dL [2.2 mmol/L] vs $\geq$ 85 mg/dL) and by geographical region.

Evolocumab and placebo will be blinded Central laboratory results of the lipid panel, ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded post-treatment and not reported to the investigator until unblinding of the clinical database. Investigators should not perform non-protocol testing of these analytes during a subject's study participation and until at least 12 weeks after the subject's last

administration of IP or the end of study, whichever is later. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated. The study includes collection of biomarker samples, unless prohibited by local law or regulations, and, where approved by the independent ethics committee and/or institutional review board (IEC/IRB) and applicable regulatory and other authorities, all subjects will be invited to consent to pharmacogenetic analyses. The study will end when at least 1630 subjects have experienced a key secondary endpoint event of cardiovascular death, myocardial infarction, or stroke. Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product (IP) administration. Vital status should be obtained periodically and must be obtained at the end of the study for all subjects unless prohibited by local law.

All deaths and components of primary and secondary endpoints (myocardial infarction, stroke, revascularization, hospitalization for unstable angina, hospitalization for heart failure, and transient ischemic attack [TIA]) will be adjudicated by an independent external Clinical Events Committee (CEC), using standardized definitions. In addition, new onset diabetes will also be adjudicated. An external independent Data Monitoring Committee (DMC) will formally review the accumulating data from this and other ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. An Executive Committee (EC) has been formed to advise Amgen on trial design and implementation, to conduct confirmatory data analyses at the end of the trial, and for assistance in the communication of trial results. The EC is co-chaired by 2 external academic cardiologists who are experts in lipids and/or clinical trials and includes at least 3 additional external members with similar expertise. An external independent Lipid Monitoring Committee (LMC) will be formed to review unblinded lipid results by treatment group to ensure design parameters are being met. The LMC will be advisory to Amgen and the EC. It will not have access to clinical outcomes data. The LMC may review treatment compliance and other relevant non-outcomes data. It may recommend increasing the number of randomized subjects or the duration of treatment and follow-up. A similar LMC is a design characteristic of an ongoing study for lipid lowering with ezetimibe/simvastatin combination therapy. In addition, the LMC may be involved in the follow-up for subjects meeting lipid (eg, triglycerides) alert thresholds by the central laboratory. Analyses for the DMC and LMC will be provided by the Independent Biostatistical Group (IBG), which is external to Amgen. Details for each committee will be provided in a committee charter.

3.2 Sample Size

The calculation of sample size is based on the first secondary endpoint in this study (triple composite of cardiovascular death, myocardial infarction, or stroke) and assumes a placebo event rate of approximately 2% per year (LaRosa et al, 2005; Cannon et al, 2004; de Lemos et al, 2004; Pedersen et al, 2005; SEARCH et al, 2010; Wiviott et al, 2007; Stone et al, 2011; Alberts et al, 2009; Baigent et al, 2011; MarketScan database [population; Thomson Reuters Healthcare Inc., Ann Arbor, MI 48018, USA]; United Health Care database [population; OptumInsight, Eden Prairie, MN 55344, USA), a 26-month enrollment period, and a total 3% of loss to follow-up rate over the study duration of approximately 56 months. The hazard ratio for the triple composite endpoint in this study design is assumed to be 0.8. It is an estimate based on the recent CTT Collaboration (2010) meta-analysis which assessed the relationship between LDL-C reduction and the cardiovascular events concluded that the relative risk decreases by 1% for every 1.8 mg/dL reduction in LDL-C. However, it is assumed that the attenuation of treatment effect will occur because of a 3-month treatment lag at the beginning of the trial and non-compliance of 10% per year during the course of the study. The overall type I error is controlled at a 0.05 significance level. After accounting for these factors, and based on a two-sided log-rank test of demonstrating the superiority of evolocumab over placebo, a total sample size of 27,500 subjects, with approximately 1630 subjects experiencing a key secondary endpoint event, is required to ensure approximately 90% power (Shih, 1995). Assuming an annualized event rate of approximately 4.5% and a hazard ratio of 0.8 for the primary endpoint, at the time of 1630 key secondary events observed among total of 27,500 subjects, there will be approximately 3550 primary events observed which will ensure a power of 99.8% to demonstrate superiority of evolocumab over placebo in the primary endpoint.

Based on the accumulating event rate in the pooled treatment groups, the sample size may be altered in order to complete the trial with at least 1630 key secondary events observed in approximately 56 months. Alternatively, Amgen may choose to lengthen the study duration to ensure at least 1630 key secondary events observed and other assumptions are met.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoint

The primary endpoint is the time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first. (Note: The primary endpoint includes ischemic and hemorrhagic stroke)

4.1.2 Secondary Endpoints

The key secondary endpoint is:

- time to cardiovascular death, myocardial infarction, or stroke, whichever occurs first

Other secondary endpoints are:

- time to cardiovascular death
- time to death by any cause
- time to first myocardial infarction (fatal or non-fatal)
- time to first stroke
- time to first coronary revascularization
- time to cardiovascular death or first hospitalization for worsening heart failure, whichever occurs first
- time to ischemic fatal or non-fatal stroke or TIA, whichever occurs first

4.1.3 Exploratory Endpoints

- Time to coronary death
- Total number of events from the components of the primary endpoint (myocardial infarction, hospitalization for unstable angina, stroke, coronary revascularization, and cardiovascular death)
- LDL-C response (LDL-C $<$ 70 mg/dL [1.8 mmol/L]) at each scheduled assessment
- Change and percent change from baseline at each scheduled assessment in each of the following parameters:
  - LDL-C
  - Total cholesterol
  - non-HDL-C
  - ApoB
  - Total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio
  - Triglycerides
  - VLDL-C

  - HDL-C
  - ApoA1
  - Lp(a)

- Change from baseline in PCSK9 at each scheduled assessment
- HbA1C at each scheduled assessment
- hsCRP at each scheduled assessment

4.1.4 Safety Endpoints

- Subject incidence of treatment emergent adverse events
- Safety laboratory values and vital signs at each scheduled assessment
- ECG parameters (such as RR, PR, QRS, QT and QTc intervals) at each scheduled assessment
- Incidence of anti-evolocumab antibody (binding and neutralizing) formation

4.1.5 Pharmacokinetics Endpoints

- Serum concentration of evolocumab at selected time points

4.2 Planned Covariates

Covariates include, but not limited to:

- Stratification factors:
  - The final screening LDL-C level
    - < 85 mg/dL [2.2 mmol/L]
    - ≥ 85 mg/dL
  - Geographical region
    - Europe - all European countries, Israel
    - North America - US and Canada
    - Latin America
    - Asia Pacific - all Asian countries, Australasia, and South Africa.
- Age at study enrollment (< 65 years, ≥ 65 years)
- Sex
- Race (White, non-white)
- Prior MI: (No**,** < 1 year, 1-< 2 years, ≥ 2 years)
- Baseline PCSK9 level
- Baseline LDL-C
- Ezetimibe use at baseline (yes, no)

5. Hypotheses and/or Estimations

5.1 Primary

The primary hypothesis is that additional LDL-C lowering with evolocumab when used in addition to other treatment for dyslipidemia is well tolerated and decreases the risk of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization in subjects with clinically evident cardiovascular disease.

5.2 Secondary

Secondary hypotheses are that additional LDL-C lowering with evolocumab when used in addition to other treatment for dyslipidemia

- decreases the risk of cardiovascular mortality, myocardial infarction, or stroke
- decreases the risk of cardiovascular mortality
- decreases the risk of all-cause mortality
- decreases the risk of myocardial infarction
- decreases the risk of stroke
- decreases the risk of coronary revascularization
- decreases the risk of cardiovascular mortality or hospitalization for worsening heart failure
- decreases the risk of fatal or non-fatal ischemic stroke or transient ischemic attack

6. Definitions

6.1 Study Endpoints

Coronary death

Coronary death is defined as cardiovascular death of adjudicated reasons as acute MI or sudden cardiac.

6.2 Study Time Points

Randomization Date

The randomization date for each subject is the date the investigator (or designee) confirms in the IVRS that the subject has met all eligibility criteria and is randomized.

Enrollment Date

The enrollment date is the same as the randomization date. The enrollment data is a derived field on eCRF page.

Study Day 1

The date of the first investigational product (IP) administration or the date of enrollment for subjects who are not administrated any dose of IP.

Study Day

For each subject and 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).

First Dose Date of Investigational Product

For each subject, the first dose date of investigational product is defined as the date of the first administration of investigational product (evolocumab or placebo)

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 investigational product (evolocumab or placebo).

Subject End of Study (EOS) Date

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

Overall-trial Study End Date

The study end date is the last end of study date of all randomized subjects.

Start Date of EOS Visit Period (SDEVP)

The study is event driven. Amgen and the Executive Committee will monitor the overall event rate and will set the start date for the EOS visit period based on the anticipated date when approximately 1630 subjects will have experienced an adjudicated key secondary endpoint.

End Date of EOS Visit Period (EDEVP)

The end date of EOS visit period is approximately 10 weeks from SDEVP.

Subject Last Non-fatal Potential Endpoint Collection Date (LPEPD)

This definition is defined for each subject and related to censoring schema. The detail definition is described in Appendix D.

Vital Status

Vital status will be recorded using the following 2 approaches:

- For subjects who died on study, the vital status will be recorded on the EOS eCRF with an EOS reason of death and an EOS date as the date of death reported by site.
- For subjects who withdraw early from the study with reasons other than death, an assessment of vital status will be performed during the EOS visit period, as allowed by local law. Data will be recorded on the EOS Vital Status (EOSVS) eCRF and/or the Long Term Follow-Up/Survival Status eCRF (separate from the EOS eCRF).

Death recorded from both approaches will be a potential endpoint and adjudicated by the CEC.

Subject Last Confirmed Survival Status Date (LCSSD)

This definition is related to censoring schema and the detail definition is described in Appendix D.

Censoring date

Endpoints will be censored differently according to the endpoint and specific analysis being conducted. The details of censoring schema are described in Appendix D.

Time-to-event Definition

Only events adjudicated as positive and occurred prior to or on the LCSSD are included in the time-to-event analysis.

- For subjects who experienced such event,
  - event = yes (ie, censor = no)
  - time-to-event (days) = adjudicated onset date – randomization date + 1
- For subjects who do not experienced such event,
  - event = no (ie, censor = yes)
  - time-to-event (days) = censoring date – randomization date + 1

6.3 Demographics and Baseline Related Definitions

Age

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

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 randomization date. If for any reason only 1 value is available, then that value will be used as baseline.

Other Baseline Values

For ECG, the baseline value is defined as the mean over all non-missing triplicate averages of 3 (or all available) readings from each set of triplicate taken prior to or on randomization date.

For PCSK9, the baseline value is defined as the last non-missing value collected prior to or on study day 1.

For targeted concomitant medications data, the medication taken at baseline is defined as the medication collected at day 1 visit (ie, currently medications taken at time of day 1 visit).

For all other variables, the baseline value is defined as the last non-missing value collected prior to or on randomization date.

Change from Baseline

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

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

Percent Change from Baseline

The percent change from baseline for a given variable a given time point is defined as:

100 × [(value at given time point – baseline value) / baseline value]

Baseline Metabolic Syndrome

Based on the eCRF data of history of metabolic syndrome (yes, no).

Baseline major risk factors based on the protocol and eCRF data:

- diabetes (type 1 or type 2)
- age ≥ 65 years at randomization (and ≤ 85 years at time of informed consent)
- MI or non-hemorrhagic stroke within 6 months of screening
- additional diagnosis of myocardial infarction or non-hemorrhagic stroke excluding qualifying MI or non-hemorrhagic stroke

- current daily cigarette smoking
- history of symptomatic PAD (intermittent claudication with ABI < 0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease) if eligible by MI or stroke history

Baseline minor risk factors based on the protocol and eCRF data:

- history of non-MI related coronary revascularization
- residual coronary artery disease with ≥ 40% stenosis in ≥ 2 large vessels
- Most recent HDL-C < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women by central laboratory before randomization
- Most recent hsCRP > 2.0 mg/L by central laboratory before randomization
- Most recent LDL-C ≥ 130 mg/dL (3.4 mmol/L) or non-HDL-C ≥ 160 mg/dL (4.1 mmol/L) by central laboratory before randomization
- metabolic syndrome

6.4 Other Study Related Definitions

Analytical Study Week Assignments

Analytical windows will be used to assign parameters to study weeks. The algorithm is provided in Appendix A.

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.

Two Consecutive LDL-C Values < 25 mg/dL

The algorithm for defining the 2 consecutive LDL-C values < 25 mg/dL separated by at least 21 days is summarized below:

1) For each blood sample draw date that has at least one LDL-C value, identify the lowest LDL-C value
    a. If UC values exist regardless of the presence of calculated LDL-C values, the lowest UC LDL-C value will be used
    b. If only calculated LDL-C values exist, the lowest calculated LDL-C value will be used
2) If a subject has 2 consecutive (separated by at least 21 days) LDL-C values that are < 25 mg/dL, then the subject will be considered as a subject with two consecutive LDL-C values < 25 mg/dL.

IP Exposure Period in Months

For subjects whose last IP dose is Q2W:

IP Exposure Period = [min (Last IP Dose Date + 14 days, EOS Date) - First IP Dose Date + 1]/ 365.25 * 12

For subjects whose last IP dose is QM:

IP Exposure Period = [min (Last IP Dose Date + 28 days, EOS Date) - First IP Dose Date + 1]/ 365.25 * 12

Study Exposure Period in Months

For each randomized subject, Study Exposure Period = (EOS Date – Randomization Date + 1) / 365.25 * 12

Treatment Emergent Adverse Event (TEAE)

Treatment emergent adverse events are adverse events occurring between the first dose of IP and EOS. Treatment emergent adverse events can be identified if the values of the AE eCRF question “Did event start before first dose of investigational product?” is No or missing.

Target IP TEAE (On-treatment IP TEAE)

Treatment emergent adverse events are adverse events occurring from the first dose of IP date to 30 days after the last dose of IP date or EOS whichever occurs first.

Reflexive Approach for LDL-C and VLDL-C

For all analyses related to LDL-C and VLDL-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 and UC VLDL-C value from the same blood sample will be used instead, if available.

7. Analysis Subsets

7.1 Primary Analysis Set

The primary analysis set in this study is the Full Analysis Set (FAS), which is defined as all randomized subjects. Efficacy analyses will be performed on FAS. All subjects will be analyzed according to their randomized treatment assignment.

7.2 Safety Analysis Set

Safety analyses will be performed on Safety Analysis Set which is defined as all randomized subjects who received at least one dose of investigational product. For safety analyses, subjects will be grouped according to their randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

7.3 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) is defined as the subjects receiving at least 1 dose of investigational product and without pre-specified, selected important protocol deviations (IPD) thought to impact on efficacy analyses. The PPAS may be used for the sensitivity analyses of key efficacy analyses. The selected IPDs are as following:

- Violation of the selected important protocol inclusion / exclusion criteria (Appendix E)
- Use of prohibited treatment for inhibition of PCSK9 other than study provided investigational product during the study as described in protocol Section 6.7
- Subject randomized to the placebo arm but received evolocumab during the study

7.4 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all subjects with at least one evolocumab or PCSK9 serum concentration results.

7.5 ECG Analysis Set

The ECG Analysis Set will include approximately 5000 subjects at selected sites that have been provided with centralized ECG services equipment specifically for this study.

7.6 Subgroup Analyses

The following subgroups will be used for subgroup analyses for primary and key secondary efficacy endpoints.

- Stratification factors:
  - The final screening LDL-C level
    - $<$ 85 mg/dL [2.2 mmol/L]
    - $\geq$ 85 mg/dL
  - Geographical region
    - Europe - all European countries, Israel
    - North America - US and Canada

  - Latin America
  - Asia Pacific - all Asian countries, Australasia, and South Africa.

- Age at study enrollment (< 65 years, ≥ 65 years)
- Sex
- Race (white, non-white)
- Prior non-hemorrhagic stroke (yes, no)
- Symptomatic PAD (yes, no)
- Prior MI (No, < 1 year, 1-< 2 years, ≥ 2 years)
- Baseline PCSK9 level (< median, ≥ median)
- Baseline LDL-C by quartiles (Q1, median, Q3)
- Baseline HDL-C by quartiles (Q1, median, Q3)
- Baseline triglycerides by quartiles (Q1, median, Q3)
- Baseline hsCRP (< 2 mg/L, ≥ 2 mg/L)
- Ezetimibe use at baseline (yes, no)
- ACC/AHA high statin background therapy intensity at baseline (yes, no)
- History of type 2 diabetes (yes, no)

8. Interim Analysis and Early Stopping Guidelines

No formal interim analysis is planned for this study.

An Independent Biostatistics Group (IBG) will perform the analysis and provide the report to an independent Data Monitoring Committee (DMC). The DMC will review all available safety and efficacy data periodically. The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and Data Monitoring Group will not have any direct contact with study center personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be stored in the Amgen official document management system at the conclusion of the study. Further details are provided in the DMC charter.

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

Amgen's Clinical Data Management 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 enrolled 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 missing visit, or non-evaluability of a data point or an endpoint at a particular point in time. All attempts will be made to capture missing or partial data for this trial prior the database lock.

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

For all time-to-event endpoints (for examples, primary and secondary endpoints), there will be no imputation of the data, except for incomplete dates of the events. For all other efficacy and safety endpoints, unless specified otherwise, missing data will not be imputed.

9.3.2 Handling of Incomplete Dates

Missing and partially missing dates will be queried. Partial/missing onset dates (adjudicated by CEC) of time-to-event endpoints will be imputed using the following algorithm, with the reference date being the randomization date.

- Impute the missing year as the year of the reference date
- Impute the missing month as January
- Impute the missing day as 1st

If any of the resulting dates are prior to the reference date, the imputed date will be reset to the reference date. Any imputed death dates will be the maximum of (the imputed all event dates, subject EOS dates, and subject last confirmed alive date recorded on the long term survival follow-up/survival status and EOSVS eCRF page).

Adverse event and concomitant medication ([eg, lipid regulatory medication] collected start date data) with completely or partially missing start dates will be queried. After the

issue is queried, 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

For historical events (eg, date of historical MI or stroke in the targeted medical history) that will be used to summarize as baseline data, the imputation rules are as follows: if the day is missing, default to 1; if both month and day are missing, default to Jan 1. If the imputed date is on or after the randomization date, default to randomization date minus 1. Missing years will not be imputed under any condition.

9.4 Detection of Bias

This study has been designed to minimize potential bias by the use of stratified randomization of subjects into treatment groups and the use of blinding. It is not expected that any study conduct procedures or statistical analyses will introduce bias in the study results or conclusions. However, potential sources of bias in this study include:

- Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- Subject level unblinding before final database lock and formal unblinding
- DMC or LMC related analyses
- Informative censoring

Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the Clinical Study Report (CSR). Sensitivity analysis may be conducted using the per protocol analysis set (see Section 7.3).

Any inadvertent breaking of the blind 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.

For DMC related analyses, details of access to subject level treatment assignments are provided in the protocol, Section 10.3. An external independent Lipid Monitoring Committee (LMC) will be formed to review unblinded lipid results by treatment group to ensure design parameters are being met. It will not have access to clinical outcomes data. Analyses for the DMC and LMC will be provided by the Independent Biostatistical Group (IBG), which is external to Amgen. Details for each committee will be provided in a committee charter. Any additional unblinding beyond protocol specified will be documented in the CSR. No impact from the DMC and LMC's review of unblinded data is expected since all of DMC members, LMC members, and the IBG supporting DMC are independent to the Amgen study team and the study's Executive Committee.

Reasons for study withdrawal will be summarized in the CSR. If there is a differential study withdrawal rate (lost to follow-up or full consent withdrawn) between treatment arms, then the impact on primary and secondary endpoints will be explored.

Additional sensitivity analyses may be included to assess the impact of the biases on the primary and secondary endpoints. 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

Statistical assumptions for each planned method of analysis will be assessed. If the distributional or other assumptions are not met, then transformations, alternative parametric models, or nonparametric 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 and S-plus.

10. Statistical Methods of Analysis

10.1 General Principles

The study will conclude when approximately 1630 subjects have experienced a key secondary endpoint event of cardiovascular death, myocardial infarction, or stroke. At that time, the database will be cleaned, processed and a snapshot will be taken; the study will also be unblinded. Based on the snapshot, unless specified otherwise, efficacy analyses will be performed on the FAS by randomized treatment group; and safety analyses will be performed on the safety analysis set.

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

All continuous variables will be summarized using descriptive statistics, including the number of observations (n), mean, standard deviation (SD), standard error (SE), median, the 1st (Q1) and 3rd (Q3) quartiles, minimum, and maximum. All categorical variables will be summarized using the number and percent of subjects.

Missing data will not be imputed for safety endpoints.

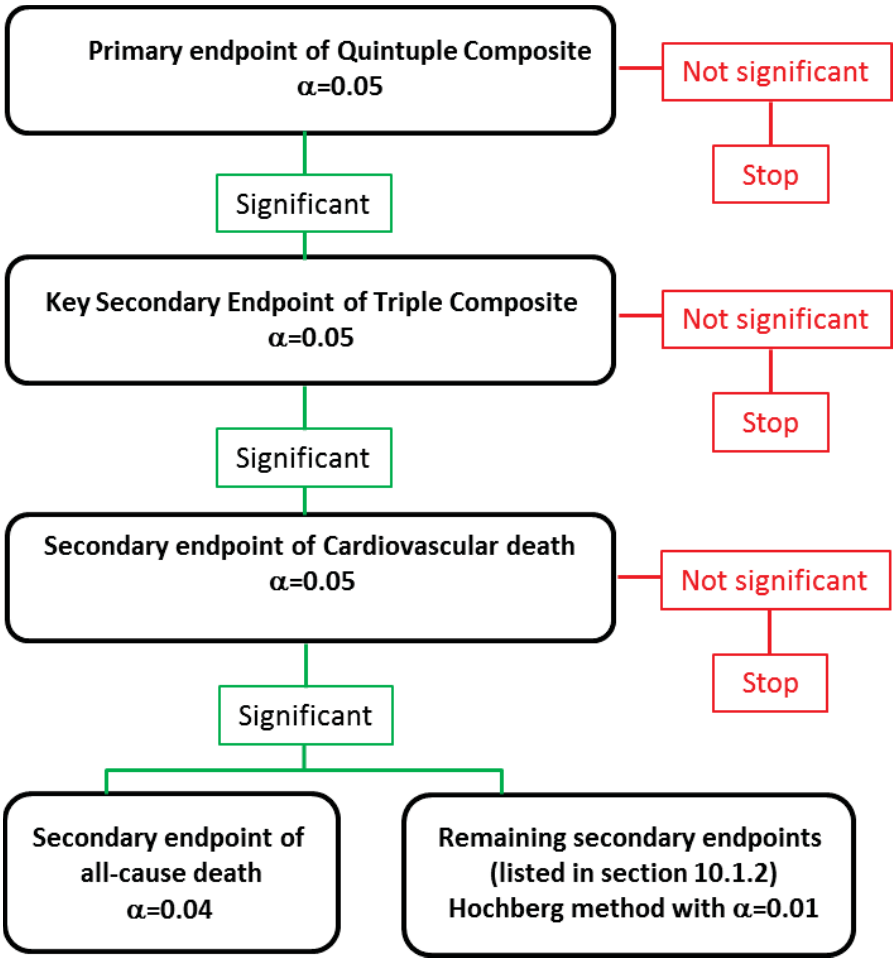
All deaths and major cardiovascular events, including the individual components of primary and secondary endpoints (myocardial infarction, stroke, revascularization, hospitalization for unstable angina, hospitalization for heart failure, and TIA) will be adjudicated by an independent external Clinical Events Committee (CEC), using standardized definitions. In addition, new onset diabetes will be adjudicated by the same CEC. The CEC is external to Amgen and primarily comprises both academic clinical physicians (to include cardiologists) and medical reviewers trained on the clinicaltrial protocol, the CEC charter, and CEC processes. The chairman of the CEC is responsible for overseeing the operations in conformance with the CEC charter and for supervising the flow of data between the sponsor/data management and the CEC. Committee members are qualified in the appropriate subspecialty and free of conflict of interest. The CEC is blinded to treatment allocation and reviews events according to pre-specified criteria defined in the CEC charter.

Multiplicity Adjustment Method

In order to preserve the overall type I error rate at 0.05 in the final analysis of the primary and secondary endpoints, the following multiplicity adjustment approach will be applied: The primary endpoint (quintuple composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, and coronary revascularization) will be compared by the treatment groups at a significance level of 0.05. If the primary endpoint reaches statistical significance at the 0.05 level, the key secondary endpoint (composite of cardiovascular death, myocardial infarction, and stroke) will be tested at a significance level of 0.05. If the key secondary endpoint reaches statistical significance level of 0.05, then the endpoint of cardiovascular death will be tested at a significance level of 0.05. If the endpoint of cardiovascular death reaches statistical significance level of 0.05, the following testing will be conducted in parallel under the weighted Bonferroni split:

- The endpoint of all-cause death will be tested at a significance level of 0.04.
- Other remaining secondary endpoints (time to first myocardial infraction, time to first stroke, time to first coronary revascularization, time to cardiovascular death or first hospitalization for worsening heart failure, and time to fatal or non-fatal ischemic stroke or TIA) will be tested at an overall significance level of 0.01 applying the Hochberg method (Hochberg, 1988).

No multiplicity adjustment will be used for exploratory or sensitivity analyses. The multiplicity adjustment for primary and secondary endpoints is shown in the following flowchart:



10.2 Subject Accountability

The number of subjects screened, randomized, receiving IP, and completing the study will be summarized by randomized treatment group. Study discontinuation and IP discontinuation will be tabulated separately by reasons for discontinuation. The time of withdrawal from IP and study (with reasons other than death) will be analyzed graphically by treatment arm. The number of subjects included in and excluded from each analysis set will 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

All baseline tables will be summarized by randomized treatment group and for all subjects in FAS. Baseline tables will summarize the following: baseline characteristics, demographics, targeted medical history, laboratory parameters, and lipid regulating medication. If multiple races have been reported for a subject, the subject will be categorized as multiple race.

10.5 Efficacy Analyses

FAS will be used as the primary analysis set for the primary analysis of the primary and secondary efficacy endpoints. For each subject, the date of randomization will be used as the starting point for all time-to-event calculation. For each event, the onset date adjudicated by CEC will be used as event onset date for time-to-event calculation. Subject incidence of potential endpoint event and adjudicated events will be summarized. For subjects who discontinued study early (due to consent withdraw or loss-to-follow up), their vital status data will be collected during EOS visit period and prior to the overall-trial study end date. All adjudicated death cases collected up to the overall-trial end date of EOS visit period (EDEVP; defined in section 6.2) will be summarized based on CEC adjudicated results (CV deaths, non-CV deaths, and undetermined deaths).

Primary analyses of the primary and secondary efficacy endpoints will include the events from the subject randomization date to the subject EOS date. In addition, for subjects with consent withdrawal, death events occurring between the subject consent withdrawal date and the overall-trial end date of EOS visit period (EDEVP; defined in section 6.2) will be included in analyses of composite and mortality endpoints.

The details of event coverage and censoring schema are described in Appendix D.

For covariate and subgroup analyses, the stratification factors from the eCRF will be used. Differences in stratum assignment between IVRS and eCRF will be tabulated.

10.5.1 Analyses of Primary Endpoint

The primary endpoint is the time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first.

10.5.1.1 Primary Summary and Analysis Method of Primary Endpoint

The primary analysis for this endpoint will employ the intent-to-treat (ITT) principle and use a survival analysis. Subject count by event status will be provided by treatment

group. For each treatment group, Kaplan-Meier (K-M) curves will be estimated and graphically displayed. For primary analysis, the 2 survival functions will be compared using a 2-sided log-rank test stratified by randomization stratification factors collected via IVRS. K-M estimates and 95% CIs will be calculated by randomized treatment for event time if applicable. In addition, the hazard ratio and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors collected via IVRS.

10.5.1.2 Sensitivity Analysis of Primary Endpoint

1) The primary analysis of the primary endpoint will be repeated using the SDEVP instead of the individual LPEPD (see Appendix D).
2) If applicable, subgroup analyses on the primary endpoint will be conducted using the subgroups listed in Section 7.6. The purpose of the subgroup analyses is to confirm that the treatment effect is consistent within various subgroups. The interaction between each subgroup and the treatment group will be evaluated. A forest plot will be created to summarize the variability in the hazard ratios across subgroups.
3) Covariate analyses of the primary endpoint using Cox model will be performed as sensitivity analysis. Baseline covariates listed in Section 4.2 will be included in the model one at a time.
4) The trend and consistency of the treatment effect on the components of the primary endpoint will be examined and tested for heterogeneity by using the Wei-Lin-Weissfeld (WLW) method (Wei et al, 1989). Time of each component endpoints are:
    a. Time to CV death
    b. Time to first MI
    c. Time to first Stroke
    d. Time to first hospitalization for unstable angina
    e. Time to first coronary revascularization
5) To assess the impact of critical protocol deviations, primary analysis of the primary endpoint may also be repeated using the PPAS if more than 5% subjects have experienced a pre-specified IPD (see Section 7.3).
6) The proportional hazards assumption in the Cox model will be assessed by the following 2 methods:
    a. Visual inspection of parallel lines in the log(-log(survival)) vs log of survival time graph (Hosmer, 1999)
    b. Including randomized treatment group as a time dependent covariate in the Cox model by creating interactions of log(time) and treatment group

Inference from the Cox model is generally fairly robust with modest violation of the proportional hazards assumption, however, a piecewise Cox model with 1-year intervals will be considered if there is evidence of a strong non-proportionality.

7) The primary analysis of the primary endpoint will be repeated using the on-treatment analysis. On-treatment analysis will only include the events that occurred within 30 days of the last dose of IP or subject LCSSD date, whichever is earlier. The censoring schema for subjects without an event in this sensitivity analysis is described in Appendix D.

8) The sensitivity analysis of the primary endpoint will be repeated using LCSSD. The censoring schema in the sensitivity analysis is described in Appendix D.

9) If the discrepancy in stratum assignment between IVRS and eCRF occurred in more than 5% subjects, the primary analysis will be repeated with stratifying the model by the stratification from eCRF.

10.5.2 Analyses of Key Secondary Efficacy Endpoint

The key secondary endpoint is time to cardiovascular death, myocardial infarction, or stroke, whichever occurs first. The key secondary endpoint will be analyzed as per the primary endpoint including the primary analysis and sensitivity analyses where applicable (see Section 10.5.1).

10.5.3 Analyses of Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints described in Section 4.1.2 will be analyzed per the primary analysis of the primary endpoint.

Sensitivity analysis (1) stated in Section 10.5.1 will be performed for each of other secondary endpoints.

The following component events will be analyzed using similar methods as the primary analysis of the primary endpoint. No multiplicity adjustment will be used for these 2 component events.

- Time to hospitalization for worsening heart failure
- Time to TIA

10.5.4 Analyses of Exploratory Endpoints

Exploratory endpoints are time to coronary death, total number of events from the components of the primary composite endpoint, and measurements of lipid.

Time to coronary death

Time to coronary death will be analyzed in the same way as the primary analysis for time to cardiovascular death endpoint.

Total number of events from primary composite endpoint (recurrent events)

Summary statistics for the total number of primary endpoint events will be provided.

The negative binomial (NB) model adjusting for randomization stratification factors collected via IVRS will be used for treatment comparison.

Other continuous endpoints including lipid parameters

For lipid parameters and other selected lab parameters listed in Section 4.1.3., they will be summarized as follows:

The repeated measures linear mixed effects model for lipid parameters will be used to compare the percent change from baseline between treatment groups by using all measurements from baseline up to EOS. The model will include terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear mixed effects model is used. If missing values are > 10% of total measurements, ad hoc sensitivity analyses will be performed to evaluate the impact of missing values due to early withdrawal from IP. Summary statistics of change and percent change of lipid parameters from baseline will be provided. Subgroup and covariate analyses of change and percent change of LDL-C will be performed for the following:

- Geographical region (a stratification factor)
  - Europe - all European countries**,** Israel
  - North America - US and Canada
  - Latin America
  - Asia Pacific - all Asian countries, Australasia, and South Africa.
- Age at study enrollment (< 65, >= 65)
- Sex
- Race (White, non-white)
- Baseline LDL-C by quartiles (Q1, median, Q3)

Categorical lipid parameters

LDL-C response (LDL-C < 70 mg/dL [1.8 mmol/L]) at each scheduled assessment will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factors.

10.6 Safety Analyses

Safety Analysis Set will be used as the analysis set for the safety analyses. The Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 or later will be used to code all adverse events (AE) to a system organ class and a preferred term. Severity of AEs will be graded using the CTCAE (Appendix B) and recorded on the eCRF. All adverse event tables will be summarized by treatment group.

10.6.1 Treatment Emergent AEs and AEs of Interest

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

Subject incidence of all treatment-emergent AEs (TEAEs), serious AEs, and AEs leading to withdrawal of investigational product will be tabulated by system organ class and preferred term in descending order of frequency. The overall summary of target IP TEAE will be also presented.

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.

Subgroups group analyses for age group (< 65, ≥ 65), sex, and race (if appropriate) will be presented by system organ class and preferred term in descending order of

frequency. All races with less than 5% of the total enrolled subjects will be pooled together for summary purposes.

Subject incidence of EOIs will be summarized according to the EOI search strategy categories defined by the EOI steering committee. Unless specified otherwise, EOI tables based on both narrow and broad search strategies will be provided. The definition of each EOI may be modified and new EOIs may be added based on findings from ongoing pharmacovigilance. Updates of the search strategy due to MedDRA upgrades or other reasons may not trigger a SAP amendment. However, the most recent EOIs per Amgen EOI search strategy will be used at the time of the analysis and these search terms will be included in an appendix of the study report. As of the date of preparing this version, the current EOIs are:

- potential hypersensitivity events
- potential injection site reaction events
- potential muscle events
- potential neurocognitive events
- potential demyelination events
- potential hepatitis C infection
- transaminase elevations and potential hepatic disorders

10.6.2 Safety Analysis of Low LDL

The safety analyses (TEAE, serious AE, and EOIs) will be summarized for subjects with any postbaseline LDL-C and all postbaseline LDL-C with the cutoffs of 25 mg/dL and 40 mg/dL and all postbaseline LDL-C $\geq$ 40 mg/dL. In addition, the safety analyses will be summarized in subjects with 2 consecutive postbaseline LDL-C $<$ 25 mg/dL separated by at least 21 days.

10.6.3 Adjudicated Positive Hyperglycemic Events

The potential hyperglycemic events are adjudicated by an independent external CEC. Subject incidence of the adjudicated positive hyperglycemic events for all randomized subjects in the safety analysis set will be summarized by treatment group. In addition, subject incidence of the positive adjudicated hyperglycemic events among subjects with baseline metabolic syndrome and the following groups will be summarized by treatment group.

- baseline normoglycemia
- baseline Impaired fasting glucose
- baseline normoglycemia or impaired fasting glucose

10.6.4 Safety Analyses for Subjects With Type I Diabetes at Baseline

Subject incidence of all treatment-emergent AEs (TEAEs), serious AEs, AEs leading to withdrawal of investigational product, and target IP TEAEs will be tabulated by system organ class and preferred term in descending order of frequency for the subjects with type I diabetes.

Descriptive statistics will be provided for actual values and changes from baseline in fasting glucose and HbA1c for the subjects with type I diabetes at baseline.

10.6.5 Laboratory Test Results

Descriptive statistics will be provided for actual values and changes from baseline in each laboratory parameter at each protocol-specified scheduled visit. Laboratory analytes are provided in the protocol Table 4. Lab shift tables using the most current version of the CTCAE grading will be used for the selected analytes of interest, when applicable.

In addition, CK and liver function test (LFT) abnormalities will be assessed by the incidence overall and by visit for the following categories:

- CK $>$ 5 x ULN
- CK $>$ 10 x ULN
- ALT or AST $>$ 3 x ULN
- ALT or AST $>$ 5 x ULN
- Total bilirubin $>$ 2 x ULN
- (ALT or AST $>$ 3 x ULN) and Total bilirubin $>$ 2 x ULN and Alkaline Phosphatase $<$ 2 x ULN

10.6.6 Vital Signs

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

10.6.7 Electrocardiogram (ECG)

For post-baseline assessments where ECG is performed in triplicate, the average of the 3 (or all available) readings will be used for analysis. Observations with the following diagnosis or findings will be excluded from analysis: artificial pacemaker, atrial fibrillation, atrial flutter, left bundle branch block, and right bundle branch block.

PR, QRS, QT, QTc (ie, QTcB and QTcF) and RR intervals and their change from baseline will be summarized for each treatment group by scheduled visit. In each treatment group, subjects will be categorized and summarized per their maximum

post-baseline absolute QTc interval using limits of 450 ms, 480 ms, and 500 ms. They will also be categorized per their maximum change from baseline QTc interval using limits of 30 ms and 60 ms.

10.6.8 Antibody Formation

The incidence and percentages of subjects who develop anti-AMG145 antibodies (binding and neutralizing) at any time will be tabulated.

10.6.9 Exposure to Investigational Product

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

10.6.10 Exposure to Other Protocol-specified Treatment

The number and proportion of subjects receiving protocol specified lipid regulating medications captured on the Statin Therapy Administration eCRF will be summarized by treatment group. The subject incidence of changes in protocol specified background lipid regulating medications during the treatment period will also be provided by randomized treatment group.

10.6.11 Exposure to Concomitant Medication

The number and proportion of subjects receiving targeted concomitant medications will be summarized. Summaries will be provided for baseline use and use after Study Day 1.

11. Changes from Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

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13. Appendices

Appendix A. Analytical Study Week Assignments

Lipid parameters, vital signs, and other lab parameters 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, with scheduled visit time being the center of each interval. The mapping intervals for all distinct schedules are summarized in the following table.

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 study day of that specific study week (7×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.

Scheduled Visit Week	Scheduled Visit Day	Vital Signs Target Therapy	Chemistry Coagulation Hematology	Weight , Urinalysis HbA1c	Lipid Panel	ApoA1 ApoB Lp(a)	hsCRP	Anti-bodies	PK[d], PCSK9[d], 12 lead ECG
Week 2	15	(randomization date, 21]							
Week 4	29	(21, 56]			(randomization date, 56]				
Week 12	85	(56, 126]	(randomization date,126]		(56, 126]	(randomization date, 126]			(randomization date,126]
Week 24	169	(126, 210]	(126,252]	(randomization date,252]	(126,252]	(126,252]		(randomization date,252]	(126,966]
Week 36	253	(210, 294]							
Week 48	337	(294, 378]	(252,420]	(252,420]	(252, 420]	(252,1050]	(randomization date, 1050]	(252, 504]	
Q12W[a]	n*7+1	((n-6)*7, (n+6)*7]							
Q24W[b]	m*7+1		((m-12)*7, (m+12)*7]	((m-12)*7, (m+12)*7]	((m-12)*7, (m+12)*7]				
Q48W[c]	q*7+1							((q-24)*7, (q+24)*7]	

Note:
[a] For Q12W scheduled visit, n=60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228.
[b] For Q24W scheduled visit, m=72, 96, 120, 144, 168, 192, 216.
[c] For Q48W scheduled visit, q=96, 144, 192.
[d] study day 1 used (rather than randomization date)

Appendix B. Common Terminology Criteria for Adverse Events

Refer to the NCI Common Terminology Criteria for AEs (CTCAE) Version 4.0, published: May 28, 2009 (v4.03: June 14, 2010) for AE and lab grading and information. The CTCAE is available at the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix C. Lipid Modifying Background Therapy

Based on ACC/AHA guidelines:

	HIGH-INTENSITY STATIN THERAPY	MODERATE-INTENSITY STATIN THERAPY	LOW-INTENSITY STATIN THERAPY	Notes (classification of atypical doses)
Atorvastatin	40 mg or greater QD	10 mg QD up to less than 40 mg QD	Less than 10 mg QD	Atorvastatin 30 mg QD is Moderate intensity.
Rosuvastatin	20 mg or greater QD	5 – < 20 mg QD	less than 5 mg QD	Rosuvastatin < 5 mg QD is low intensity , Rosuvastatin 15 mg QD = moderate
Simvastatin	80 mg or greater QD	20-80 mg QD	< 20 mg QD	And Simvastatin > 40 and < 80 mg QD is moderate, Simvastatin 80 mg or greater QD = high, Simvastatin < 20 mg QD is low-intensity
Pravastatin		40 mg or greater QD	less than 40 mg QD	Pravastatin < 10 mg QD is low intensity
Lovastatin		40 mg or greater QD	less than 40 mg QD	Lovastatin 80 mg QD = moderate, Lovastatin 10 mg QD = Low-intensity
Fluvastatin		80 mg QD	less than 80 mg QD	Fluvastatin 10 mg QD = Low-intensity
Pitavastatin		≥ 2 mg QD	< 2 mg QD	

UNKNOWN-INTENSITY STATIN THERAPY if dose frequency is other or dose unit is other and therefore total daily dose in mg cannot be derived; NO STATIN THERAPY if subject does not use any statin at baseline.

Appendix D. Time-to-Event Endpoint Censoring Schema

Objective

This schema is to describe how time-to-event endpoints are censored in the final analysis.

Executive summary of the Censoring Dates Used in the Primary Analysis

Table 2 summarizes the definitions of deriving the key censoring dates (subject LPEPD and subject LCSSD).

Table 2. Derivation of Key Censoring Dates

	Subject LPEPD (Last non-fatal PEP Collection Date)	**Subject LCSSD (Last Confirmed Survival Status Date)**
Derivation		
EOS reason as consent withdrawal		
Subjects with either long term follow-up/survival status eCRF page or EOSVS eCRF pages	Subject EOS date (date of consent withdrawal)	* Adjudicated death date if exists * Otherwise, min (last known alive date, EDEVP)
Subjects with neither long term follow-up/survival status eCRF page nor EOSVS eCRF pages	Subject EOS date (date of consent withdrawal)	Subject EOS date (date of consent withdrawal)
EOS reasons not consent withdrawal		
Subjects with either long term follow-up/survival status eCRF page or EOSVS eCRF pages	* Last non-fatal PEP ascertainment date if exists * Otherwise, subject last vital sign collection date prior to the earliest contact date on either form	* Adjudicated death date if exists * Otherwise, min (last known alive date, EDEVP)
Subjects with neither long term follow-up/survival status eCRF page nor EOSVS eCRF pages	* Adjudicated death date if exists * Otherwise, subject EOS date	* Adjudicated death date if exists * Otherwise, subject EOS date

Definitions

Subject Last Non-fatal Potential Endpoint Collection Date (LPEPD)

For each subject, LPEPD is defined based on the following mutually exclusive categories:

- For subjects whose EOS reason is consent withdrawal, their LPEPD is subject EOS date (ie, date of consent withdrawal).
- For subjects whose EOS reason is not consent withdrawal, their LPEPD is defined as the followings:
    - For subjects who have either Long Term Follow-up/Survival Status eCRF or EOSVS eCRF pages, their LPEPD is
        - last non-fatal PEP ascertainment date if exists
        - otherwise, subject last vital sign collection date prior to the earliest of contact date on either form
    - For subjects who do not have both Long Term Follow-up/Survival Status eCRF and EOSVS eCRF pages, their LPEPD is
        - Adjudicated death date if exists;
        - Otherwise, subject EOS date

Note for Long Term Follow-Up/Survival Status eCRF and EOSVS eCRF:

- Both forms collect vital status and ascertainment of all non-fatal PEPs.
    - Last non-fatal PEP ascertainment date is the latest date that sites evaluates subjects whether having non-fatal PEPs or not. If all questions of the non-fatal PEP occurrence are left blank in an eCRF page, it implies the non-fatal PEP ascertainment is not done since last review.

- Subjects who discontinued investigational products and agreed to be followed-up should have
    - Long Term Follow-Up/Survival Status eCRF pages.
    - EOSVS pages unless the subject dies before SDEVP.

Subject Last Confirmed Survival Status Date (LCSSD)

- For subjects whose EOS reason is consent withdrawal
    - For subjects who have either Long Term Follow-Up/Survival Status eCRF or EOSVS eCRF pages, their LCSSD is defined as follows:
        - the adjudicated death date if exists;
        - otherwise, the minimum (last known alive date from either form, EDEVP)
    - For subjects who do not have both Long Term Follow-Up/Survival Status eCRF and EOSVS eCRF pages, their LCSSD is subject EOS date (date of consent withdrawal).

- For subjects whose EOS reason is not consent withdrawal
    - For subjects who have either Long Term Follow-Up/Survival Status eCRF or EOSVS eCRF pages, their LCSSD is defined as follows
        - the adjudicated death date if exists;
        - otherwise, the minimum (last known alive date from either form, EDEVP)
    - For subjects who do not have both Long Term Follow-Up/Survival Status and EOSVS eCRF pages, their LCSSD is defined as follows:
        - adjudicated death date if exists
        - otherwise, subject EOS date

Categories of Time-to-event Endpoint

All time-to-event endpoints in this study are categorized in Table 3. Censoring approach will vary depending on the category of the endpoint.

Table 3. Category of Time-to-event Endpoint

Category	Endpoint
Composite	• time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first • time to cardiovascular death, myocardial infarction, or stroke, whichever occurs first • time to cardiovascular death or hospitalization for worsening heart failure, whichever occurs first • time to ischemic fatal or non-fatal stroke or transient ischemic attack, whichever occurs first • time to the first (fatal or non-fatal) myocardial infarction • time to the first (fatal or non-fatal) stroke
Non-mortality	• time to the first coronary revascularization
Mortality	• time to cardiovascular death • time to coronary death • time to death by any cause

Event Coverage and Censoring Date for Subjects without an Event

Table 4 is presented for event coverage and censoring date algorithm for subjects without an event in both primary and sensitivity analyses. For subjects without an event, endpoints will be censored differently according to their category and the specific analysis being conducted (see Table 4):

- For composite endpoints with both mortality and non-mortality components, as well as for other non-mortality endpoints, the censoring date will be the subject LPEPD date in the primary analysis. The censoring date will be followings for various sensitivity analyses:
    - the earlier of the LPEPD date and the SDEVP in the sensitivity analysis (SDEVP). This sensitivity analysis will be implemented for the primary and secondary endpoints.
    - the earlier of the LPEPD date and 30 days after the last dose of IP in the sensitivity analysis (on-treatment). This sensitivity analysis will be implemented for the primary and key secondary endpoint.
    - the subject LCSSD in the sensitivity analysis (LCSSD). This sensitivity analysis will be implemented for primary and key secondary endpoint.
- For mortality endpoints, the censoring date will be subject LSCCD in the primary analysis, and the earlier of the LCSSD and the SDEVP in the sensitivity analysis (SDEVP).

Table 4. Event Coverage and Censoring Date for Subjects Without an Event

		Sensitivity Analysis		
	Primary Analysis	SDEVP [a]	On-treatment [b]	LCSSD [b]
Event coverage	Events ≤ LCSSD	Events ≤ Min (LCSSD, SDEVP)	Events ≤ Min (LCSSD, last IP dose date + 30 days)	Events ≤ LCSSD
Censoring date for subjects without events				
Composite or Non-mortality	LPEPD	min(LPEPD, SDEVP)	min(LPEPD, last IP dose date + 30 days)	LCSSD
Mortality	LCSSD	min(LCSSD, SDEVP)	NA	NA

[a] Applicable to the primary and all secondary endpoints
[b] Applicable to the primary and key secondary endpoint

Figure 1. Mortality Endpoints Censoring in the Primary Analysis

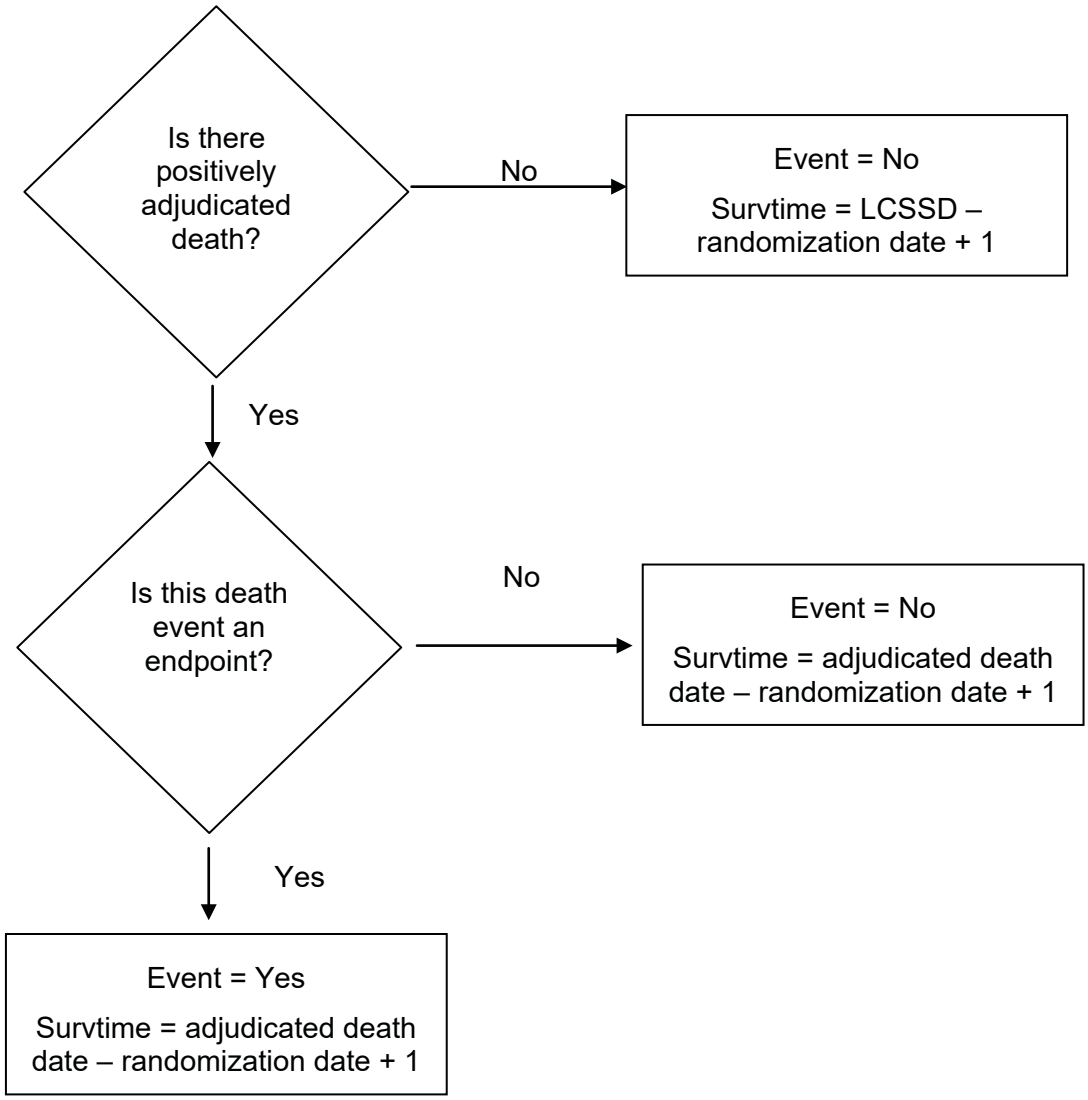
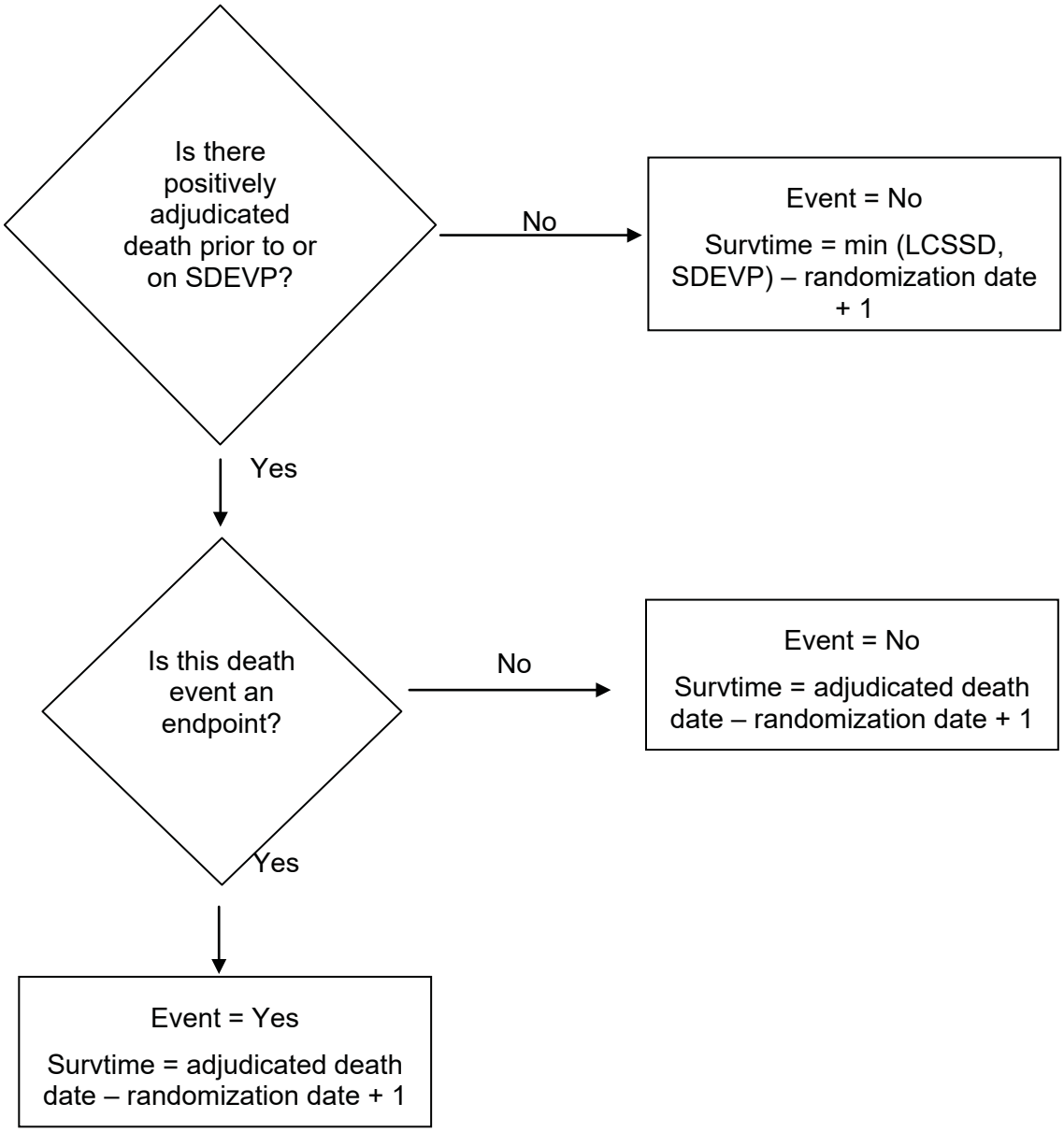


Figure 2. Mortality Endpoints Censoring in the Sensitivity Analyses



Appendix E. Selected IPD list

IPD Description
No informed consent
No history of clinically evident cardiovascular disease
Known hemorrhagic stroke
Uncontrolled or recurrent ventricular tachycardia
Planned cardiac surgery or revascularization within 3 months of randomization
Active liver disease or hepatic dysfunction
Severe concomitant non-cardiovascular disease
Screening CK > 5 times ULN
Currently or recently enrolled in another study
Known sensitivity to treatment
Unable to give informed consent and/or comply