STATISTICAL ANALYSIS PLAN

Protocol Title:	**A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145**
Short Protocol Title:	**An Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145**
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SAP Date:	**Document Version** **Date** **Original (v[1.0])** 23 Febuary 2012 **Amendment (v [2.0])** 22 FEB 2018

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AHA	America Heart Association
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AUC_t	Area under the curve over the dosing interval
CEC	Clinical Events Committee
CHD	Coronary Heart Disease
C_{max}	Maximum observed concentration
CSR	Clinical study report
CTCAE	NCI Common Terminology Treatment Collaboration
ECG	Electrocardiogram
EOI	Events of Interest
EOS	End of study
FAS	Full analysis set
HDL/LDL RATIO	High density lipoprotein/low density lipoprotein ratio
HDL-C	High density lipoprotein cholesterol
HR	Heart Rate
hsCRP	High sensitivity C-reactive protein
IBG	Independent biostatistical group
IC	Informed Consent
IP	Investigational product (AMG 145)
IPD	Important protocol deviation
IVRS	Interactive voice response system
LDL-C	Low density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
MedDRA	Medical dictionary for regulatory activities
NCA	Noncompartmental analysis
NCEP ATP III	National Cholesterol Education Panel Adult Treatment Panel III (see References)
NYHA	New York Heart Association
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
PKDM	Pharmacokinetics and drug metabolism
Q4W	Every 4 weeks
SC	Subcutaneous

Abbreviation or Term	Definition/Explanation
SOC	Standard of care
SD	Standard deviation
T_{max}	Time to maximum observed concentration
UC	Ultracentrifugation
VLDL-C	Very low density lipoprotein cholesterol

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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 7 for AMG 145 Study 20110110 – OSLER dated 12 November 2015. The scope of this plan includes the final analysis that are planned and will be executed by the Biostatistics department or designee unless otherwise specified, eg, standard PK tables will be provided by clinical pharmacology modeling and simulation (CPMS).

2.   Objectives

2.1   Primary

To characterize the safety and tolerability of long-term administration of AMG 145

2.2   Secondary

Secondary objectives are:

- To characterize the efficacy of long-term administration of AMG 145 as assessed by low density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio in subjects with hypercholesterolemia

2.3   Exploratory

Exploratory objectives are:

- To assess the percent change in fasting plasma lipids (non-HDL-C, apolipoprotein B, total-cholesterol/HDL-C ratio, total cholesterol), and ApoB/ApoA1 ratio, triglycerides, Lp(a), and high sensitivity C-reactive protein (hsCRP)
- To investigate potential biomarker development by biochemical analysis of blood samples
- To characterize pharmacokinetics of AMG 145 and proprotein convertase subtilisin/kexin type 9 (PCSK9) levels
- To estimate cardiovascular event rates in subjects treated with AMG 145 in aggregated exploratory analyses across the AMG 145 program

3.   Study Overview

3.1   Study Design

This is a multicenter, controlled, open-label extension study to assess the long-term safety and efficacy of AMG 145. Subjects that complete a qualifying protocol will be randomized 2:1 to two treatment groups: Monthly AMG 145 (420mg QM) + standard of care (SOC) or SOC alone for the first year of the study. During the first 12 weeks of the study (blinded post-randomization stabilization period), LDL-C will remain blinded and subjects will remain on the background lipid lowering therapy from the parent study. After 12 weeks, LDL-C will be unblinded and subjects may receive additional

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lipid-lowering therapy based on local standards of care. Subjects in the SOC only arm will not receive AMG 145 or a placebo injection for the first year of the study. Randomization should occur at the end of the parent study's end of study (EOS) visit or within 3 days after the parent study's EOS visit and will be stratified by the treatment arm the subject was randomized to in the parent study. Investigators, site staff, subjects, and the study team will be blinded to on-study lipid levels until week 12 (1st quarterly) visit of this study. At the end of the first year (week 52), starting at week 56 (week4/year 2) all subjects will receive open-label AMG 145 for up to 4 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subjects' decision to discontinue for any reason, or until an administrative decision is made to close the study).

3.2   Sample Size

The number of subjects entering this study will depend on the number of subjects completing their respective AMG 145 parent studies and willingness to enroll. Approximately 2000 (1970) subjects will be randomized in the qualifying parent studies. Assuming 80% of these subjects enroll in this extension study, the sample size will be approximately 1600 (1576).

The exact 95% confidence intervals for a 5% incidence rate under various enrollment assumptions using the binomial distribution for particular adverse events are provided in the table below. The estimates are derived using SAS version 9.2.

Percent of Subjects Enrolling	Total Number of Subjects Reporting Adverse Event	Estimated Adverse Event Incidence Rate	
		Incidence Rate	95% Confidence Interval
60	59/1182	5%	(4%, 6%)
70	69/1379	5%	(4%, 6%)
80	79/1576	5%	(4%, 6%)
90	89/1773	5%	(4%, 6%)

4.   Study Endpoints and Baseline Covariates

4.1   Primary Endpoint

Subject incidence of adverse events

4.2   Secondary Endpoints

- LDL-C at week 24 and week 52
- non-HDL-C at week 24 and week 52

- ApoB at week 24 and week 52

- Total cholesterol/HDL-C ratio at week 24 and week 52

- ApoB/ApoA1 ratio at week 24 and week 52

4.3   Exploratory Endpoints

- Subject incidence of adjudicated events

    – Death (all cause, cardiovascular)

    – Cardiac ischemic events (myocardial infarction, hospitalization for unstable angina, coronary revascularization)

    – Hospitalization for heart failure

    – Cerebrovascular events (transient ischemic attack, stroke)

- Subject incidence of non-coronary revascularization

- Change and percent change from baseline at each scheduled visit in each of the following lipid parameters:

    – Total cholesterol

    – non-HDL-C

    – LDL-C

    – ApoB

    – total cholesterol/HDL-C ratio

    – ApoB/ApoA1 ratio

    – Triglycerides

    – HDL-C

    – VLDL-C

    – ApoA1

    – Lp(a)

    – hsCRP

- PCSK9 at each scheduled visit

4.4   Safety Endpoints

- Changes from baseline in safety laboratory values (including clinical chemistry and hematology) and vital signs at each scheduled visit

- Subject incidence of anti-AMG 145 antibodies

4.5   Pharmacokinetics Endpoints

- Serum concentration of AMG 145 at selected time points

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4.6   Planned Covariates

Covariates include, but not limited to:

Stratification Factor

- randomized to AMG 145 Q2W in parent study
- randomized to AMG 145 Q4W in parent study
- not randomized to AMG 145 in parent study

Baseline Covariates from Parent Study

- Demographics
  - age (< 65, ≥ 65)
  - gender
  - race (black, white, and other)
  - region (North America, other)
  - Body Mass Index (BMI) (< 25, $25 - < 30$, ≥ 30)
  - Weight ($<$ baseline median, $\geq$ baseline median)
- Medical history
  - diabetes mellitus (yes, no)
  - hypertension (yes, no)
  - current smoker (yes, no)
  - metabolic syndrome per modified AHA/NHLBI criterion (yes, no)
  - baseline CHD risk factors ≥ 2 (yes, no)
  - family history of premature coronary heart disease (yes, no)
- Concomitant medication and laboratory measurement
  - Lipid modifying background therapy (intensive statin usage, non-intensive statin usage, non-statin usage, none [as defined in Appendix D])
  - LDL-C ($<$ baseline median, $\geq$ baseline median)
  - Triglycerides ($<$ baseline median, $\geq$ baseline median; < 150 mg/dL, ≥ 150 mg/dL, < 200 mg/dL, ≥ 200 mg/dL)
  - PCSK9 level ($<$ baseline median, $\geq$ baseline median)

5.   Hypothesis

There is no formal hypothesis testing. Subject incidences of adverse events will be estimated.

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6.   Definitions

6.1   Study Time Points

Baseline

Baseline is defined as the parent study baseline.

First Dose Date

For subjects randomized to AMG 145+SOC, the first dose date is the first date at which the subject was administered IP. For subjects randomized to SOC, the first dose date is the first date at which the subject was administered IP at or after the Week 56 visit.

End of Investigational Product (EOIP) Date

If a subject has completed or discontinued IP, the EOIP date is date recorded on the final IP dose date eCRF.

End of Study (EOS) Date

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

Enrollment Date

The enrollment date for a subject is either the subject's EOS date for the parent study or the randomization date for Study 20110110, whichever is later.

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.

Study Day 1

For subjects randomized to AMG 145 plus SOC arm and received at least one dose of AMG 145, Study Day 1 is defined as the first day that AMG 145 is administered during this study.

For subjects randomized to SOC only arm, or randomized to AMG 145 plus SOC arm but never received AMG 145, Study Day 1 is defined as the randomization date or parent EOS date, whichever is later.

Study Day

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

Study day = (study visit date – Study Day 1 date) + 1

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

Study day = (study visit date – Study Day 1 date)

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SOC-Controlled period

The start of the SOC-Controlled period is the Study Day 1.

For end of the SOC-Controlled period:

- If a subject is administered a dose of IP at the Week 56, the day prior to the week 56 IP date is the end of the SOC-Controlled period.
- If a subject is not administered a dose of IP at Week 56, the SOC-Controlled period will end at the earliest of Study Day 399, and the EOS date.

All-IP period

Subjects with EOS dates ≤ end of SOC-Controlled period dates will have missing start and end of All-IP period dates.

Otherwise:

- All-IP period start date = end of SOC-Controlled period date+1.
- All-IP period end date = EOS date.

6.2   Demographics and Baseline Related Definitions

Change (absolute change) from Baseline

The arithmetic difference between a post-randomization value and baseline for a given time point: Change from baseline = (post-randomization 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 change from baseline / baseline value

6.3   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.

IP Exposure Period in Months

IP Exposure Period in months= [(min(EOIP date + 28 days, EOS date) – First dose date) + 1] / 365.25 * 12. For subjects randomized to SOC treatment during the SOC-Controlled period, the first dose date is equivalent to the first dose date during the All-IP period.

Study Exposure Period in Months

For each randomized subject, Study Exposure Period in months = [EOS date – enrollment date) + 1] / 365.25 * 12

IP Exposure in Months During the SOC-Controlled period

For subjects randomized to AMG 145+SOC arm and received at least one dose of AMG 145 in the SOC-Controlled period, IP Exposure during the SOC-Controlled period = [(min(EOIP date + 28 days, end of SOC-Controlled period) – Study Day 1) + 1] / 365.25 * 12. Any IP exposure < 0 will be considered as N/A.

For subjects randomized to SOC or randomized to AMG 145 + SOC and not dosed in the SOC-Controlled period, IP Exposure during the SOC-Controlled period = N/A.

IP Exposure in Months During the All-IP period

For each randomized subject in the Interim All-IP period Analysis Set, IP Exposure during the All-IP period

= [(min(EOIP + 28 days, end of All-IP period) – start date of All-IP period) + 1] / 365.25 * 12. If the above calculation is < 0, then set to 0.

Study Exposure in Months During the SOC-Controlled period

For each randomized subject, Study Exposure Period for the SOC-Controlled period = [(end of SOC-Controlled period date – start of the SOC-Controlled period + 1] / 365.25 * 12.

Study Exposure in Months During the All-IP period

For each randomized subject that received a dose of IP during the All-IP period,

Study Exposure Period for the All-IP period = [(end of All-IP period – start of the All-IP period + 1] / 365.25 * 12.

Adverse Events Included in the Summary Tables

An adverse event is included in SOC-Controlled period summaries if it occurs during the SOC-Controlled period and the subject is in the Full Analysis Set.

An adverse event is included in All-IP period summaries if it occurs during the All-IP period and the subject is in the All-IP period Analysis Set.

Baseline Metabolic Syndrome

For each subject without type 2 diabetes mellitus, metabolic syndrome is identified by the presence of 3 or more of the components listed below (modified AHA/NHLBI criteria). Subjects with type 2 diabetes cannot be categorized as having metabolic syndrome.

Risk Factor	Defining Level

Elevated waist circumference:
Non-Asian:
  Men
  Women
Asian:
  Men
  Women
	
	≥ 102 cm
	≥ 88 cm
	
	≥ 90 cm
	≥ 80 cm

Triglycerides	≥ 150 mg/dL

HDL cholesterol
  Men
  Women
	
	< 40 mg/dL
	< 50 mg/dL

Blood pressure	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg OR Hypertension checked 'yes' on CV Medical History eCRF
Fasting glucose	≥ 100 mg/dL

4-Level Treatment Group

All tables in the full analysis set in the final analysis will be summarized by randomization group (AMG 145+SOC vs. SOC alone). Since subjects received either AMG 145 or control treatment in parent study, the tables will be further categorized as the following 4 levels (parent study treatment group/current study treatment group):
"AMG 145/AMG 145 + SOC"; "AMG 145/SOC Only"; "Control/AMG 145 + SOC", and "Control/SOC Only".

7.   Analysis Subsets

7.1   Primary Analysis Set

Full Analysis Set

The full analysis set (FAS) will include all subjects randomized in this study. All analyses of the randomized controlled period of the study will be performed using the FAS. Analyses of the period after the randomized controlled period may be limited to those receiving investigational product.

The All-IP Period Analysis Set

The All-IP analysis set (AAS) will include all subjects that were randomized in this study and dosed with IP and on-study in the All-IP period. Data will be summarized analyzed from the start of the All-IP period to EOS.

Steroid Analysis Set

The steroid analysis set (SAS) includes all subjects who participate in the steroid substudy.

8.   Interim Analysis and Early Stopping Guidelines

An administrative interim analysis, which included pharmacokinetic / pharmacodynamics (PKPD) modeling and was based on accumulated efficacy and safety data from this and other concurrently conducted studies with AMG 145, was performed by an internal unblinded group to guide future clinical development plans. Members in the designated internal unblinded group did not have direct roles or responsibilities in conducting any study included in this administrative interim analysis. There was an additional 1-year interim analysis to summarize the data collected in the randomized study period (up to week 52) after all subjects had completed the week 52 visits. There were no plans to modify or discontinue this study based on the results of the interim analysis. Also, additional analysis may be performed periodically throughout the study after parent studies are closed and individual subjects are unblinded to their lipid values.

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. 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 selected endpoints will be assessed through descriptive summaries of the measurements over time.

9.3.2   Missing Lipid Panel Endpoint

There will be no imputation for missing lipid panel endpoint.

9.3.3   Handling of Incomplete Dates

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	1st	Default to Study Day 1 if an event starts the same year and month as Study Day 1
	Day and Month	1st Jan	Default to Study Day 1 if an event started the same year as Day 1

9.4   Detection of Bias

A factor that may bias the results of the study is major protocol deviations likely to impact the analysis and interpretation of the endpoints. Important protocol deviations likely to impact the analysis and interpretation of the endpoints will be tabulated in the Clinical Study Report (CSR).

If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, 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 variables. Extreme data points will be identified during the review of the data prior to database lock. Such data points will be reviewed with clinical data management to ensure accuracy. All analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

9.6   Distributional Characteristics

There are no distributional requirements for the planned analyses. Therefore no assessment will be made.

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

Statistical analyses in this open label extension study will be descriptive in nature. No statistical inference is planned.

Subject disposition, demographics and baseline characteristics will be summarized.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. For categorical variables, the frequency and percentage will be given.

Final analyses will be based on data collected from this study and baseline/some EOS data from the parent studies. Descriptions of any integrated analyses with the parent studies are out of scope for this SAP.

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 a snapshot will be taken. All endpoints will be

analyzed based on this snapshot. For all endpoints, results will be summarized by the treatment group to which subjects are randomized to in this study, unless otherwise specified. Subjects will be further categorized according to whether they were randomized to AMG 145 or not in their parent study. For the SoC-Controlled period, this combined treatment group will have 4 levels (parent study treatment group/year 1 treatment group): "AMG 145/AMG 145 + SOC"; "AMG 145/ SOC only"; "Not AMG 145/AMG 145 + SOC", and "Not AMG 145/SOC only". For the All-IP period, subjects will be further categorized according to year 1 treatment group: " SoC in SoC-Controlled Period/AMG 145 + SOC"; "AMG 145 + SOC in SoC-Controlled Period/AMG 145 + SOC".

Unless specified otherwise, the baseline value is defined as the subject's baseline value from the parent study.

All analyses will be carried out separately for the FAS and the AAS analysis sets, unless specified otherwise. There will be no imputation for missing data. Deaths and major cardiovascular events from this study will be adjudicated by an independent Clinical Events Committee (CEC) to facilitate aggregated analyses across the program. These events adjudicated by the CEC include:

− death by any cause
− cardiovascular death
− myocardial infarction
− hospitalization for unstable angina
− coronary revascularization
− stroke
− hospitalization for heart failure
− transient ischemic attack (TIA)
− non-coronary revascularizations

10.2   Subject Accountability

The number and percent of subjects who were randomized, received IP, completed IP, discontinued investigational product and reasons for discontinuing, completed study, and discontinued study and reasons for discontinuing will be summarized by treatment group and for the SOC-controlled and All-IP periods separately as well as overall.

10.3   Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject visit and updated during the IPD reviews throughout the study prior to

database lock. If a snapshot is being taken during the study rather than a database lock at the end of the study, categories should be 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. The final IPD list is used to produce the Summary of IPDs table (see Section 12.1) and the List of Subjects with IPDs (see Section 12.2).

10.4   Demographic and Baseline Characteristics

All baseline tables will be summarized by randomized treatment and for all subjects in the FAS and AAS. Baseline tables will summarize the following: baseline characteristics, demographics, cardiovascular medical history, and laboratory parameters.

All demographics and baseline variables will be populated from the parent studies.

These tables will summarize the following:

- Parent study
- Stratification factor (randomized to AMG 145 Q2W in parent study; randomized to AMG 145 Q4W in parent study; not randomized to AMG 145 in parent study)
- Demographics
    - age (years)
    - age group (< 65, ≥ 65)
    - gender
    - ethnicity
    - race
    - region (North America, Other)
- Characteristics
    - height (cm)
    - weight (kg)
    - body mass index (kg/m^2)
- Targeted medical history
    - coronary artery disease (including angina, myocardial infarction [MI], coronary artery bypass graft [CABG], and percutaneous coronary intervention [PCI])
    - cerebrovascular or peripheral arterial disease (including transient ischemic attack [TIA], stroke, carotid or vertebral artery disease, and peripheral arterial disease)
    - atrial fibrillation/flutter (current or former)
    - congestive heart failure (current NYHA class)
    - left ventricular systolic function

- cardiac devices/pacemakers
- metabolic syndrome
- CHD risk factors
- Laboratory parameters
    - LDL-C (UC and calculated)
    - Total cholesterol
    - non-HDL-C
    - ApoB
    - Total cholesterol/HDL-C ratio
    - ApoB/ApoA1 ratio
    - Triglycerides
    - Lp(a)
    - ApoA1
    - VLDL-C
    - HDL-C
    - hsCRP
    - PCSK9
    - Vitamin E
    - Steroids
- Lipid-regulating concomitant medications

10.5   Analyses of Primary Endpoint

10.5.1   General Principles

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later will be used to code all adverse events (AE) to a system organ class and a preferred term. All analyses will be performed separately for the FAS and AAS analysis sets.

Subject incidence of adverse events, 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.

Summaries of adverse events and serious AEs 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 adverse events associated with injectable protein therapies Hypersensitivity or allergic reactions and potential hepatitis C infections will be summarized by category and preferred term.

Subgroup analyses for stratification factor, 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.

10.6   Analyses of Secondary and Exploratory Endpoints

10.6.1   Analyses of Secondary Endpoints

The secondary endpoints of percent change and absolute change from baseline will be summarized for each scheduled visit by randomized treatment group in this study and also the combined treatment group (4 levels). All analyses will be performed separately for each of the FAS and AAS analysis sets.

10.6.2   Analyses of Exploratory Endpoints

All analyses will be performed separately for the SOC-Controlled period and the All-IP period.

Subject incidence of adjudicated CV endpoints will be summarized. The percent change and change from baseline in laboratory based exploratory endpoints at each scheduled visit will be summarized. For continuous exploratory endpoints, treatment group summary statistics (number of subjects, mean, median, standard deviation or standard error, first and third quartiles, minimum, and maximum) at all scheduled visits will be calculated.

10.6.3   Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoint Analyses

Individual and mean serum AMG 145 and PCSK9 concentration-time profiles will be provided using nominal times. Individual and summary statistics of AMG 145 serum concentrations will be provided.

Compartmental exposure-response analyses will not be specified in this analysis plan but will be addressed in *Population Pharmacokinetic and Pharmacodynamic Analysis of AMG 145 in Subjects with Hyperlipidemia Using Data from Amgen Phase 1 and Phase 2 Studies* as a metadata analysis.

These analyses will be performed by the CPMS group.

10.7   Safety Analyses

10.7.1   Laboratory Test Results

Descriptive statistics will be provided for actual values and changes from baseline in each applicable laboratory parameter at each protocol-specified scheduled visit.

Laboratory analytes are provided in the protocol Table 7-1. Lab shift tables using the most current version of the CTCAE version v4.03 (Appendix C) or later grading will be used for the select analytes of interest, when applicable. Shift tables will be provided for the SOC-Controlled period and the All-IP period. The results will be based on the maximum (ie, worst) shift from parent basline to the end of the SOC-Controlled period and from the parent baseline to end of the All-IP period, respectively.

10.7.2   Vital Signs

Systolic and diastolic blood pressure and heart rate will be summarized using descriptive statistics at each scheduled visit. Summaries will also include the change from baseline at each scheduled visit

10.7.3   Anti-AMG 145 Antibodies

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

10.7.4   Exposure to Investigational Product

Descriptive statistics will be produced to describe the patient-month exposure to investigational product, by treatment group for both the FAS and AAS sets as well as overall.

Exposure definitions are provided in Section 6.3.

10.7.5   Exposure to Other Protocol Specified Treatment

The number and proportion of subjects receiving selected lipid regulating medications captured on the Lipid Regulating Concomitant Medications eCRF will be summarized using descriptive statistics. Summaries will be provided for baseline use and use after Study Day 1. The subject incidence of changes in lipid regulating medications during the treatment period will also be provided.

10.7.6   Exposure to Concomitant Medication

The number and proportion of subjects receiving the lipid regulating concomitant medications will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary. Summaries will be provided for baseline use and use after Study Day 1.

10.7.7   Steroid Substudy

For steroid summaries, the change will be relative to the week 0 value. Analytes for the steroid substudy (ACTH, FSH, LH, Cortisol, Testosterone, Estradiol) will be summarized for each treatment group using descriptive statistics at each scheduled visit.

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11.   Changes From Protocol-specified Analyses

A repeated measures mixed model for the secondary endpoints won't be done in the final analysis because the primary interest of the open label extension study is to characterize the safety and tolerability of long-term administration of AMG 145.

The following analysis won't be done:

Point estimates of group means and their 95% confidence intervals will be presented. Differences in the group means, along with the 95% confidence intervals, of the secondary endpoints will be estimated at each scheduled visit between:

- the AMG 145 + SOC group and the SOC only group in this study, regardless of the treatment arm the subject was randomized to in their parent study, and

- the AMG 145 + SOC group and SOC only group in this study, by whether the subject was randomized to AMG 145 or not in their parent study.

12.   Literature Citations / References

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106:3143-3421.

Grundy SM et al. Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* 2005;112:2735-2752.

Alberti KGMM et al. Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation: International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640-1645.

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13.   Data not Covered by This Plan

Currently there are no pre-planned analyses for the biochemical cardiovascular

biomarker objective.

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14.   Appendices

Appendix A. 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, with scheduled visit time being the center of each interval. The mapping intervals for all distinct schedules are summarized in the following table. Week 0 mapping does not pertain to parent study week mapping. Data from the parent studies will use the original analytical weeks in the individual study SAPs.

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). 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	Vital Signs for AMG 145+SOC group	Vital Signs for SOC only group	Fasting plasma lipids ApoA1, ApoB PCSK9 Chemistry Coagulation Hematology hsCRP, Lp(a) HbA1c	Anti-AMG 145 antibodies	Weight, Physical Exam, Urinalysis
Week 4	(1, 42]	(1, 56]	(1, 56]	(1, 56]	
Week 8	(42, 70]				
Week 12	(70, 98]	(56, 126]	(56, 126]	(56, 126]	
Week 16	(98, 126]				
Week 20	(126, 154]				
Week 24	(154, 182]	(126, 210]	(126, 210]	(126, 210]	
Week 28	(182, 210]				
Week 32	(210, 238]				
Week 36	(238, 266]	(210, 294]	(210, 294]	(210, 294]	

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Scheduled Visit Week	Vital Signs for AMG 145+SOC group	Vital Signs for SOC only group	Fasting plasma lipids ApoA1, ,ApoB PCSK9 Chemistry Coagulation Hematology hsCRP, Lp(a) HbA1c	Anti-AMG 145 antibodies	Weight, Physical Exam, Urinalysis
Week 40	(266, 294]				
Week 44	(294, 322]				
Week 48	(322, 350]	(294,350]	(294,350]	(294,350]	
Week 52	(350, End of SOC-Controlled period]	(350, End of SOC-Controlled period]	(350, End of SOC-Controlled period]	(350, End of SOC-Controlled period]	(1, End of SOC-Controlled period]
Week 56	[Beginning of All-IP period, 406]	[Beginning of All-IP period, 406]			
Week 60	(406, 434]	(406, 434]			
Week 64	(434, 462]	(434, 462]	[Beginning of All-IP period,490]		
Week 68	(462, 490]	(462, 490]			
Week 72	(490, 518]	(490, 518]			
Week 76	(518, 546]	(518, 546]	(490, 574]		
Week 80	(546, 574]	(546, 574]			
Week 84	(574, 602]	(574, 602]			
Week 88	(602, 630]	(602, 630]	(574,658]		
Week 92	(630, 658]	(630, 658]			
Week 96	(658, 686]	(658, 686]			
Week 100	(686, 714]	(686, 714]	(658, 742]		
Week 104	(714,742]	(714,742]		[Beginning of All-IP period, 910]	
Week n	([n-2]*7, [n+2]*7]	([n-2]*7, [n+2]*7]	([m-6]*7, [m+6]*7]	([q-26]*7,[q+26]*7]	
Week 260	>1806	>1806	>1806	>1638	≥Beginning of All-IP period

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Note:
n=108,112,116,120,124,128,132,136,140,144,148,152,156,160,164,168,172,176,180,
184,188,192,196,200,204,208,212,216,220,224,228,232,236,240,244,248,252,256.
m=112,124,136,148,160,172,184,196,208,220,232,244,256
q=156, 208, 260

Scheduled Visit Week	Vitamin E	Steroids
Week 0	≤1	≤1
Week 12	(1,126]	(1,126]
Week 24	(126,266]	(126,266]
Week 52	(266, End of SOC-Controlled period]	(266, End of SOC-Controlled period]
Week 76	[Beginning of All-IP period, 616]	
Week 100	(616,728]	

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 shift 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.