INTERIM STATISTICAL ANALYSIS PLAN

For Study 20120138 (Phase 3 Open-label Extension (OLE))

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Table of Contents

Page

List of Appendices

Table of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AHA/NHLBI	American Heart Association/National Heart, Lung, and Blood Institute
ALT	Alanine aminotransferase
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
CK	Creatine phosphokinase
CSR	Clinical study report
CTCAE	NCI Common Terminology Treatment Collaboration
CV	Cardiovascular
eCRF	Electronic Case Report Form
EOIP	End of investigational product
EOS	End of study
HbA1c	Glycated hemoglobin
HDL-C	High density lipoprotein cholesterol
hsCRP	High sensitivity C-reactive protein
IAAS	Interim All-IP period Analysis Set
ICOAS	Interim SOC-Controlled period Analysis Set
INR	International normalized ratio
IP	Investigational product (AMG 145)
IVRS	Interactive voice response system
LDL-C	Low density lipoprotein cholesterol
LFT	Liver Function Test
Lp(a)	Lipoprotein(a)
MedDRA	Medical dictionary for regulatory activities
OLE	Open label extension
QM	Every month
Q2W	Every 2 weeks
SOC	Standard of care
SAP	Statistical analysis plan
TIA	Transient ischemic attack
ULN	Upper limit of normal
VLDL-C	Very low density lipoprotein cholesterol

1. Introduction

The purpose of this interim SAP is to pre-specify interim analyses to support regulatory filings. The analysis strategy is consistent with the protocol specified analysis. Analyses will be performed based on datasets of an ongoing study 20120138, entitled A Multicenter, Controlled, Open-label (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145 (latest amendment 2 is 30 APR 2013).

2. Objectives

The objective for this analysis is to summarize the safety and lipid data collected up to a cutoff date reported in the table outputs for subjects rolled over from parent studies into the extension study 20120138. All data prior to the data cut date will be collected, checked and queried in the similar fashion as the final database lock.

3. Endpoints

3.1 Primary Endpoint

Subject incidence of Adverse Events (AEs).

3.2 Secondary Endpoints

- Percent change from baseline in LDL-C at each visit with planned lipid measurements
- Change from baseline in LDL-C at each visit with planned lipid measurements
- Percent change from parent study EOS in LDL-C at each visit with planned lipid measurements
- Change from parent study EOS in LDL-C at each visit with planned lipid measurements

3.3 Exploratory Endpoints

- Subject incidence of adjudicated events and non-coronary revascularization
    - 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)
    - Non-coronary revascularization
- Change and percent change from baseline and from parent study EOS at each scheduled visit in each of the following lipid and other lab parameters
    - Non-HDL-C
    - ApoB
    - Total cholesterol/HDL-C ratio
    - Total cholesterol

- ApoB/ApoA1 ratio
- Lp(a)
- Triglycerides
- HDL-C
- VLDL-C
- ApoA1
- High sensitivity C-reactive protein (hsCRP)

3.4 Other Safety Endpoints

- Changes from baseline in safety laboratory values (including HbA1c) and vital signs at each scheduled visit.
- **Development of anti-AMG 145 antibodies**

4. Hypothesis

The primary clinical hypothesis is that long-term exposure of AMG 145 will be safe and well-tolerated in subjects with primary hyperlipidemia and subjects with mixed dyslipidemia.

5. Definitions

5.1 Study Time Points

Baseline

For variables other than sex, race, country, region, and baseline metabolic syndrome, baseline is defined as the parent study baseline. Note that baseline metabolic syndrome will be using parent study baseline information, but with updated sex and race from the extension study data.

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 48 clinical visit.

End of Investigational Product (EOIP) Date

If a subject has completed or discontinued IP, the EOIP date is the 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 date that subject has signed the ICF for Study 20120138, 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+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+SOC arm but never received AMG 145, Study Day 1 is defined as the day of randomization.

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)

SOC-Controlled period

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

For the end of the SOC-Controlled period:

- If a subject is administered a dose of IP at Week 48, the day prior to the week 48 IP date is the end of the SOC-Controlled period.
- If a subject is not administered a dose of IP at Week 48, the SOC-Controlled period will end the earliest of Study Day 343, the EOS date, or data cutoff date.

All-IP period

Subjects with EOS dates or data cutoff 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 or the data cutoff date, whichever occurred earlier.

5.2 Demographic 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

Change (absolute change) from Parent EOS

The arithmetic difference between a post-enrollment value and the last lipid measurement used in the primary analysis of the parent study:

Change from parent EOS = (post-enrollment value – last observed lipid measurement used in parent primary analysis), where the last observed lipid measurement used in the parent primary analysis will be the week 6 value observed in study 20120348, the week 52 value observed in study 20110109, and the week 12 value observed in other studies. If the observation is missing, the subject will be excluded from change from parent EOS analysis of the particular analyte.

Percent Change from Parent EOS

The percent change from parent EOS for a given variable at a given time point is defined as:

100 x (change from parent EOS) / last lipid measurement used in parent primary analysis

5.3 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 = [(min(EOIP date + 28 days, EOS date, data cutoff 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 = [min(EOS date, data cutoff 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 Interim SOC-Controlled period 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 Interim All-IP period Analysis Set.

Sex

For subjects that enroll in an extension study, the subject's sex is the sex recorded on the extension study eCRF. For other subjects, the subject's sex is the sex recorded on the parent study eCRF.

Race

For subjects that enroll in an extension study, the subject's race is the race recorded on the extension study eCRF. For other subjects, the subject's race is the race recorded on the parent study eCRF.

Country and Region

For subjects that enroll in an extension study, the subject's country and region are those recorded in the extension study. For other subjects, the subject's country and region are those recorded in the parent study.

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	≥ 102 cm
Women	≥ 88 cm
Asian:	
Men	≥ 90 cm
Women	≥ 80 cm
Triglycerides	≥ 150 mg/dL
HDL cholesterol	
Men	< 40 mg/dL
Women	< 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 this interim analysis will be summarized by randomized 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 using 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".

6. Analysis Subsets

Interim SOC-Controlled period Analysis Set

The **I**nterim SOC-**Co**ntrolled period **A**nalysis **S**et (ICOAS) will include all subjects randomized in this study who have at least 12 weeks of potential follow-up (eg. subjects for whom Data Cutoff Date - Study Date for Study Day 1 + 1 > 91 days); the restriction on potential follow-up is to prevent operational bias that may occur by the increased frequency of visits during the first 12 weeks of the study. Subjects will be analyzed according to the treatment group to which they were randomized during the SOC-Controlled period. All data from the SOC-Controlled period will be summarized, regardless of possible IP discontinuation.

Interim All-IP period Analysis Set

The **I**nterim **A**ll-IP period **A**nalysis **S**et (IAAS) 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 or the data cutoff, whichever occurs first.

7. Data Screening and Acceptance

7.1 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.

7.2 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.

7.3 Handling of Missing and Incomplete Data

7.3.1 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. All attempts will be made to capture missing or partial data for this trial prior to the data cutoff date.

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

7.3.2 Missing Lipid Panel Endpoint

There will be no imputation for missing lipid panel endpoints.

7.3.3 Handling of Incomplete Dates

All adverse events will be included in adverse events summaries with the following exceptions: adverse events with complete dates occurring outside the definitions established in Section 5.3 and adverse events with partially missing dates for which there is sufficient information to determine the event occurred outside these definitions. For partially missing dates or completely missing dates for which it is impossible to determine whether the event occurred outside these definitions, the event will be treated as occurring during the SOC-Controlled period.

Concomitant medication with partially missing dates will be imputed as described below:

- If year is available but day and month are missing, the day and month for the start date will be set to the 1st of January of the onset year.
- If year and month are available but day is missing, the day will be set to the 1st of the month of the onset year.

7.4 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.

7.5 Outliers

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

7.6 Distributional Characteristics

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

7.7 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.

8. Statistical Methods of Analysis

8.1 General Principles

Statistical analyses in this open-label extension study will be descriptive. 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, first and third quartiles, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

All analyses will be carried out separately for the ICOAS and the IAAS analysis sets unless specified otherwise. There will be no imputation for missing data. Deaths and major cardiovascular events from this and other phase 3 studies 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)

In addition, non-coronary revascularizations will be collected.

8.2 Subject/Patient 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.

8.3 Demographic and Baseline Characteristics

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

8.4 Endpoint Analyses

8.4.1 Analyses of Primary Endpoint

The Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 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 ICOAS and IAAS 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.

Incidence of AEs related to a device will be tabulated by preferred term in descending order of frequency by treatment group.

Subject incidence of adverse events associated with lipid lowering therapies:

- **Diabetes-related**
- **Muscle-related**
- **Liver-related**

associated with injectable protein therapies:

- **Injection site reactions**
- **Hypersensitivity or allergic reactions**

and potential hepatitis C infections will be summarized by category and preferred term.

8.4.2 Analyses of Secondary Endpoints

The secondary endpoints for percent change and absolute change from baseline will be summarized for each scheduled visit. These secondary endpoint analyses will be repeated using change from parent EOS and percent change from parent EOS and summarized with descriptive statistics at each scheduled visit. All analyses will be performed separately for each of the ICOAS and IAAS analysis sets.

8.4.3 Analyses of Exploratory Endpoints

All analyses will be performed separately by SOC-controlled period and All-IP period.

Subject incidence of adjudicated CV endpoints and non-coronary revascularization 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.

8.4.4 Analyses of Laboratory Measurements

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. Lab shift table using the CTCAE v4.03 **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 baseline to the end of the SOC-Controlled period and from the parent baseline to end of the All-IP period, respectively.

In addition, CK and liver function test (LFT) abnormalities will be assessed by the incidence during the SOC-Controlled period and during the All-IP period:

- 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 or INR > 1.5)

8.4.5 Analyses of Vital Signs

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

8.4.6 Analyses of Anti-AMG 145 Antibody Formation

The **development of** anti-AMG145 antibodies (binding and neutralizing) at anytime will be **reported**.

8.4.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the patient-month exposure to investigational product, by treatment group for both the ICOAS and IAAS sets as well as overall. Exposure definitions are provided in Section 5.3.

8.4.8 Exposure to Concomitant Medications of Interest

The number and proportion of subjects receiving the **lipid regulating** medications of interest at Study Day 1 and post-Study Day 1 will be summarized by category and preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary.

9. Literature Citations / References

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.

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.

10. 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 tables. **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+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	Vital Signs for AMG 145+SOC group	Vital signs for SOC-only group
Week 0	**≤ 1**	**≤ 1**
Week 2	(1, 21]	
Week 4	(21, 42]	
Week 8	(42, 70]	
Week 12	(70, 126]	(1, 126]
Week 24	(126, 210]	(126, End of SOC-controlled period]
Week 36	(210, 280]	
Week 44	(280, 315]	
Week 46	(315, End of SOC-controlled period]	

Scheduled Visit Week	Vital Signs for AMG 145+SOC randomized group	Vital signs for SOC Alone
Week 48	[Beginning of All-IP period, 420]	[Beginning of All-IP period, 343]
Week 50		(343, 357]
Week 52		(357, 378]
Week 56		(378, 406]
Week 60		(406, 462]
Week 72	(420, 546]	(462, 546]
Week 84	(546, 630]	(546, 630]
Week 96	(630, 686]	(630, 686]
Week 100	(686, 707]	(686, 707]
Week 102	(707, 721]	(707, 721]
Week 104	>721	>721

Scheduled Visit Week	Subjects randomized to AMG 145 or Subjects randomized to SOC that were randomized to AMG 145 in parent study		
	Fasting plasma lipids, ApoA1, ApoB, **Vitamin E,** Chemistry, Hematology, Anti-AMG 145 antibodies, Urinalysis, Urine microalbumin	HbA1c	Body Weight, hsCRP
Week 0	**≤ 1**	**≤ 1**	**≤ 1**
Week 12	(1, 126]	(1, 126]	
Week 24	(126, End of SOC-Controlled period]	(126, End of SOC-Controlled period]	
Week 48	**[**Beginning of All-IP period, 420]	**[**Beginning of All-IP period, 532]	**[**Beginning of All-IP period, 532]
Week 72	(420, 588)		
Week 96	(588, 700]		
Week 104	**> 700**	>532	>532

Scheduled Visit Week	Subjects randomized to SOC that were randomized to control in the parent study		
	Fasting plasma lipids, ApoA1, ApoB, **Vitamin E,** Chemistry, Hematology, Anti-AMG 145 antibodies, Urinalysis, Urine microalbumin	HbA1c	Body weight, hsCRP
Week 0	**≤ 1**	**≤ 1**	**≤ 1**
Week 12	(1, 126]	(1, 126]	
Week 24	(126, End of SOC-Controlled period]	(126, End of SOC-Controlled period]	
Week 48	[Beginning of All-IP period, 378]	[Beginning of All-IP period, 378]	[Beginning of All-IP period, 532]
Week 60	(378, 462]	(378, 574]	
Week 72	(462, 588)		
Week 96	(588, 700]		
Week 104	**> 700**	>574	>532