STATISTICAL ANALYSIS PLAN

Protocol Title:	**A Multicenter, Single Arm, Open-label Study to Assess the Long-term Safety and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia**
Short Protocol Title:	**An Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia**
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SAP Date:	**Document Version** — **Date** **Original (v[1.0])** — 29 February 2012 **Amendment (v [2.0])** — **26 May 2018**

NCT Number: 01624142
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AHA	American 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)
BP	Blood pressure
CEC	Clinical Endpoint Committee
CK	Creatine kinase
CHD	Coronary heart disease
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	NCI Common Terminology Criteria for AEs
DBP	Diastolic Blood Pressure
DMC	Data monitoring committee
EAS	Evaluable analysis set
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOI	Events of interest
EOIP	End of investigational product
EOS	End of study
FH	Familial hypercholesterolemia
HDL-C	High density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolemia
HR	Heart Rate
hsCRP	High sensitivity CRP
IBG	Independent Biostatistical Group
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC/IRB	Independent Ethics Committee / Institutional Review Board
IP	Investigational product
IPD	Important Protocol Deviations

Abbreviation or Term	Definition/Explanation
IV	Intravenous
LDL-C	Low-density lipoprotein cholesterol
LLN	Lower limit of normal
LOCF	Last observation carried forward
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)
NCI	National Cancer Institute
NHLBI	National Heart, Lung and Blood Institute
NYHA	New York Heart Association
OL	Open Label
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
PKPD	Pharmacokinetic / pharmacodynamic
QM	Every month
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
UC	Ultracentrifugation
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment **6** for AMG 145 Study 20110271 dated **02 December 2015**. The scope of this plan includes the final analysis that is planned and will be executed by the Biostatistics department or designee unless otherwise specified.

2. Objectives

2.1 Primary

To characterize the safety and tolerability of long-term administration of AMG 145 among subjects with severe familial hypercholesterolemia

2.2 Secondary

- 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), **lipoprotein(a) [Lp(a)]**, apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A-1 (ApoA1) ratio, and response of LDL-C reduction (15% or greater) in subjects with severe familial hypercholesterolemia

2.3 Exploratory

- 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

3. Study Overview

3.1 Study Design

A multicenter, open-label study designed to assess the long-term safety, tolerability, and efficacy of AMG 145. **The study will continue until the date when the last subject has completed the assessments for week 260 (approximately 5 years) or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason, or until an administrative decision is made to close the study**. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP will not be reported to the investigator prior to week 8 for subjects coming from **a blinded (or blinded portion) of a parent study**, since some laboratory results may inadvertently unblind investigators to treatment assignment in the parent study, **until results from the parent study are made publically available. PCSK9 levels will be blinded until week 4. Vitamin E samples will only be blinded to investigators** and subjects in the first 96 weeks of the study.

Investigators should not perform local testing of these analytes. Study participation may be stopped for subjects that do not demonstrate minimal benefit (ie, subjects that have less than 5% LDL-C reduction from baseline while on therapy). **The study includes adjudication of deaths and specific cardiovascular events potential endpoints (PEPs) by an independent Clinical Events Committee (CEC)**.

3.2 Sample Size

An approximate total of **310** subjects will enroll into this study such that the long-term safety, **tolerability** and efficacy of AMG 145 among subjects with severe familial hypercholesterolemia can be assessed. Enrollees will be comprised of subjects from study 20110233 or qualifying Amgen protocol as well as subjects with severe familial hypercholesterolemia due to genetic causes beyond those studied in the parent (eg, gain of function mutations in PCSK9). Finally, we will also include additional subjects with homozygous familial hypercholesterolemia. If these subjects are ineligible for participation into an AMG 145 protocol they may be considered for participation; they otherwise must wait after study 20110233 has been closed.

The 95% confidence intervals for an approximate 5% incidence rate under various sample sizes using the binomial distribution for particular adverse events are provided in the table below.

Sample size	Total Number of Subjects Reporting Adverse Event	Estimated Adverse Event Incidence Rate	
		Incidence Rate	95% Confidence Interval
300	**15/300**	5%	**(3%, 7%)**
310	**16/310**	**5.2%**	**(3%, 8%)**
320	**16/320**	**5%**	**(3%, 7%)**

4. Study Endpoints

4.1 Primary Endpoint

Subject incidence of treatment emergent adverse events.

4.2 Secondary Endpoints

- Percent change in LDL-C from baseline at each scheduled visit
- Percent change in non-HDL-C from baseline at each scheduled visit
- **Percent change in Lp(a) from baseline at each scheduled visit**
- Percent change in ApoB from baseline at each scheduled visit
- Percent change in total cholesterol/HDL-C ratio from baseline at each scheduled visit

- Percent change in ApoB/ApoA1 ratio from baseline at each scheduled visit
- Response **rate** of subjects with 15% or greater reduction in LDL-C from baseline by scheduled visit

4.3 Exploratory Endpoints

- **Subject incidence of adjudicated events**
  - **death by any cause**
  - **cardiovascular death**
  - **myocardial infarction**
  - **hospitalization for unstable angina**
  - **coronary revascularization**
  - **stroke**
  - **transient ischemic attack (TIA)**
  - **hospitalization for heart failure**
- **Subject incidence of non-coronary revascularization**

Lipid and other efficacy laboratory parameters:

- **Percent change from baseline at each scheduled visit in the following parameters:**
  - **Total cholesterol**
  - **VLDL-C**
  - **HDL-C**
  - **ApoA1**
  - **Triglycerides**
- **Change from baseline at each scheduled visit in the following parameters:**
  - **LDL-C**
  - **Total cholesterol**
  - **non-HDL-C**
  - **ApoB**
  - **Total cholesterol/HDL-C ratio**
  - **ApoB/ApoA1 ratio**
  - **VLDL-C**
  - **HDL-C**
  - **ApoA1**
  - **Triglycerides**
  - **Lp(a)**
  - **PCSK9**

Safety

- Changes from baseline in safety laboratory values (including clinical chemistry and hematology, HbA1c) and vital signs at each scheduled visit
- Subject incidence of anti-AMG 145 antibodies (binding and neutralizing) formation

Pharmacokinetics

- Serum concentration of AMG 145 and PCSK9 at selected time points

5. Hypothesis

There is no formal hypothesis testing. The **primary clinical** hypothesis is that long-term exposure of AMG 145 will be safe and well tolerated in subjects with severe familial hypercholesterolemia.

6. Definitions

The study consists of four different types of subjects,

- **Homozygous FH Apheresis Subjects: Subjects who either met clinical criteria of HoFH or who had supportive genetic information; and receiving apheresis at study baseline.**
- **Homozygous FH Non-Apheresis Subjects: Subjects who either met clinical criteria of HoFH or who had supportive genetic information; and not receiving apheresis at study baseline**
- **Severe Heterozygous FH Apheresis Subjects: Subjects who didn't meet clinical criteria of Homozygous FH and who had supportive genetic information; and receiving apheresis at study baseline**
- **Severe Heterozygous FH Non-Apheresis Subjects: Subjects who didn't meet clinical criteria of Homozygous FH and who had supportive genetic information; and not receiving apheresis at study baseline**

Some of the definitions will depend on the subject type.

6.1 Study Time Points

Baseline

For parent study rollover subjects, baseline is defined as the baseline of the parent study.

For non-parent study subjects, baseline is defined as the time period before the first administration of AMG 145. In particular, for non-parent apheresis subjects, if an assessment was done both pre- and post-apheresis, only the assessment made pre-apheresis will be considered baseline.

For hemoglobin A1c, baseline is defined as the study 20110271 baseline for all subjects, as hemoglobin A1c was not collected in study 20110233.

First Dose Date of Investigational Product

For each subject, the First Dose Date of Investigational Product is defined as the first administration date of the IP in the extension study as recorded on the IP administration electronic Case Report Form (eCRF).

Study Day 1 and Date

For each subject, Study Day 1 is defined as the first day that protocol-specified investigational product is administered to the subject in the extension study. The date associated with Study Day 1 is the Study Day 1 Date.

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, **so that the day prior to Study Day 1 is Study Day -1.**

End of Investigational Product (EOIP) Date

For each subject, the end of AMG 145 is defined as the date of the last administration of investigational product. **This date is recorded on the IP administration eCRF if the final dose was taken in-clinic, or on the non-clinic final IP dose date eCRF if non-clinic.**

Parent End of Study Date

For each subject rolled over from a parent study, the Parent End of Study Date is the EOS date recorded on the parent End of Study eCRF.

End of Study (EOS) Date

For each subject, the end of study date is the date recorded on the End of Study eCRF of study 20110271.

Study End Date

The study end date is the last EOS date of all enrolled subjects.

6.2 Demographics and Baseline Related Definitions

Change (absolute 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 at a given time point is defined as:

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

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

Baseline CHD Risk Factors 2 or more (yes/no)

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

- current cigarette smoking
- hypertension
- type II diabetes mellitus

- family history of premature CHD as recoded on the eCRF form
- low HDL-C defined as baseline HDL-C < 40 mg/dL in men and < 50 mg/dL in women.

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 271 in Months

If a subject's last dose regimen is Q2W, then

IP Exposure Period = {[min(EOIP date + 14 days, EOS date) – First Dose Date +1]/365.25}*12.

If a subject's last dose regimen is QM, then

IP Exposure Period = {[min(EOIP date + 28 days, EOS date) – First Dose Date +1]/365.25}*12.

Non-HDL-C

Non-HDL-C =Total cholesterol – HDL-C

Treatment Emergent Adverse Events

Events are categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the value of the Adverse Events eCRF question "Did event start before first dose of investigational product?" is No or missing and up to including 30 days after the end of investigational product or the End of Study date, whichever is earlier.

Study Exposure Period in Months

For each subject enrolled into the extension study,

Study Exposure Period = (EOS date – study day 1 + 1) /365.25 *12

Study Cohorts

All tables will be summarized by the following study cohorts:

- Non-Apheresis at Baseline
- Apheresis at Baseline

7. Analysis Subsets

7.1 Primary Analysis Set

- The evaluable analysis set (EAS) for the final analysis includes all subjects enrolled in this study. This analysis set will be used in all the analyses unless otherwise specified.
- **HoFH Analysis Set (HAS): all subjects who received at least 1 dose of evolocumab in Study 20110271 and either met clinical criteria of HoFH or who had supportive genetic information**
  - **Evolocumab Titration Analysis Set (TAS): subjects who were exposed to evolocumab 420 mg QM for at least 12 weeks in Study 20110271 and then to evolocumab 420 mg Q2W for at least 12 weeks in Study 20110271 (all subjects in this analysis set had HoFH)**
  - **Adolescent subgroup: all adolescent subjects (ages 12 to < 18 years) who received at least 1 dose of evolocumab in Study 20110271 (all adolescent subjects had HoFH)**
- **Responder Analysis Set (RAS): subjects included in the Interim Analysis Set (IAS) who had UC LDL-C reduction >=15% at any time during study 20110233. This analysis set is only for the interim analysis but not for the final analysis.**
- **LDL Receptor Defective Analysis Set (RDAS): all LDL receptor defective subjects who received at least 1 dose of IP in study 20110233. This analysis set is only for the interim analysis but not for the final analysis.**
- **Severe FH Analysis Set (SAS): all subjects who received at least 1 dose of evolocumab in Study 20110271 and were not included in the HoFH Analysis Set**

7.2 Full Analysis Set

The full analysis set will include all subjects enrolled and dosed in this study.

8. Interim Analysis and Early Stopping Guidelines

A protocol-specified interim analysis was performed to facilitate phase 3 dose selections via an assessment of the safety, tolerability, and efficacy of 6 AMG-145-dosing regimens from the ongoing phase 2 program. 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. Final PK data for all enrolled subjects will be transferred from statistical programming to Amgen's PKDM group. 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 for the final analysis.

The frequency and pattern of missing data for endpoints will be assessed through descriptive summaries of the measurements over time. There will be no imputation for missing data.

9.3.2 Missing Lipid Panel Endpoint

There will be no imputation for missing lipid panel endpoints.

9.3.3 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 6.3 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 possible to determine whether the event occurred outside these definitions, the event will be treated as occurring during the treatment emergent period.

Adverse event and concomitant medications with completely or partially missing dates will be queried. If after the query is resolved, the date is still incomplete with year only or year and month only, the start date will be imputed as described **in the Imputation Rules for Incomplete Dates table** below:

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

9.4 Detection of Bias

This study has been designed to minimize potential bias. Investigators and staff involved with this trial should remain blinded to locally obtained lipid panels until the Week 8 visit for all subjects that transition from Part B of the parent study 20110233 or other qualifying blinded parent studies into this study. This is done to avoid potential parent study unblinding.

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

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

9.5 Outliers

Various methods, including univariate summaries, histograms, scatterplots, 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. **Unless specified otherwise, 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

Statistical analyses in this study are descriptive in nature. No statistical inference is planned. So there are no statistical assumptions made for the data distribution.

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.

10. Statistical Methods of Analysis

10.1 General Principles

Statistical analyses in this open label, single arm study are descriptive in nature. No statistical inference or missing value imputation 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. Descriptions of any integrated analyses with the parent studies are out of scope for this study.

The final analysis for the study will be **performed at the end of the study (defined as when the last subject has completed the assessments for week 260** or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason, or until an administrative decision is made to close the study). At that time, the database will be cleaned, processed and locked. All endpoints will be analyzed based on this snapshot.

For the interim analysis, subjects were summarized by the 20110233 parent rollover/non-20110233 parent rollover and assigned treatment groups in 20110233 (AMG 145 or placebo) if applicable. However, for the final analysis, subjects will be summarized based only on the apheresis status at **enrollment** when applicable described in section 6.3.

10.2 Subject Accountability

The number of subjects screened, enrolled, receiving IP, and completing the study will be summarized. Study discontinuation and IP discontinuation will be tabulated

separately by reasons for discontinuation. The number of subjects included in and excluded from each analysis set will be summarized.

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 and the List of Subjects with IPDs.

10.4 Demographic and Baseline Characteristics

All baseline tables will be summarized by study cohorts for all subjects **in the EAS, HAS and SAS**. Baseline tables will summarize the following:

- Baseline Characteristics
- Demographics
- Cardiovascular medical history
- Vital signs
- Laboratory parameters
- Fasting Vitamin E
- Lipid-regulating background therapies (eg, statin, ezetimibe)

10.5 Analyses of Primary Endpoint

10.5.1 General Principles

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. **Treatment-emergent AE is defined as in section 6.3**. Severity of AEs will be graded using the CTCAE (Appendix B) and recorded on the eCRF. All adverse event tables will be summarized by actual treatment arm.

Subject incidences of treatment-emergent adverse events (TEAE), serious TEAEs, and TEAEs leading to withdrawal of IP will be tabulated by system organ class and preferred term in descending order of frequency in all subjects. Treatment-related TEAEs will be provided in the overall AE summary.

10.5.2 Adverse Events of Interest

Subject incidence of adverse events associated with **injectable protein therapies hypersensitivity reactions or potential hepatitis C infections** will be summarized by category and preferred term **using narrow search strategy**.

10.6 Analyses of Secondary and Exploratory Endpoints

10.6.1 Analyses of Secondary Endpoints

Descriptive statistics on all endpoints at all scheduled visits and time points will be provided by apheresis status at study entry and by visit including percent change from baseline in the following lipid parameters:

- LDL-C
- non-HDL-C
- **Lp(a)**
- ApoB
- total cholesterol/HDL-C ratio
- ApoB/ApoA1 ratio
- Number and percent of patients with LDL-C reduction of 15% or greater from baseline by visits will also be provided.

For continuous endpoints, descriptive summaries including group means will be displayed. For response rate analysis, number and percent of responders at each visit will be displayed. All analyses will be performed for the HoFH and severe FH analysis sets unless specified.

- Depending on subject's apheresis status, protocol-specified visits vary.

10.6.2 Analyses of Exploratory Endpoints

To describe the effects over time of AMG 145 on change from baseline in proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and on change from baseline 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 in high sensitivity C-reactive protein (hsCRP), descriptive statistics will be provided by scheduled visits and by apheresis status at study entry. Figures will be provided for change from baseline and percent change from baseline analyses.

A shift table for hsCRP will be provided, for levels at baseline and maximum post-baseline value (< 0.1, 0.1-0.3, > 0.3 mg/dL) by **apheresis status** and genotype (HoFH vs. Non-HoFH).

HbA1c will be summarized at each scheduled assessment by **apheresis status** and genotype.

Death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, TIA, non-coronary revascularizations and hospitalization for heart failure will be adjudicated by an independent CEC. Subject incidence of adjudicated events will be summarized for each **apheresis status** and genotype.

10.6.3 Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Individual and mean serum AMG 145 and PCSK9 concentration-time profiles by dose group will be provided using nominal times. The effect of apheresis on AMG 145 and pharmacokinetics and also on PCSK9 will be examined separately. Pharmacokinetic data will be analyzed and stored in the Pharsight Knowledgebase Server (PKS) using the current version of Phoenix WinNonlin. Exploratory PK/PD analysis may be conducted separately as part of this study or may be combined with other studies in a meta-analysis.

These analyses will be performed by the PKDM group.

10.6.4 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 by **apheresis status** and genotype. Summaries will be provided for baseline use and use after study enrollment. The subject incidence of changes in lipid regulating medications during the treatment period will also be provided.

10.6.5 Exposure to Concomitant Medication

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

10.6.6 Apheresis Summaries

For all the subjects who were treated by apheresis at least once during the study, the number and proportion of subjects will be summarized by the type of change (**change in method of apheresis**, change in frequency, change in method, discontinuation of apheresis, first-time initiation of apheresis, re-initiation of apheresis, missed/skipped apheresis procedure and **other**) and primary reason of change.

10.7 Other Safety Analyses

10.7.1 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 3. Lab shift tables using the most current version of the CTCAE version 4.0 (Appendix B) grading will be used for the following analytes of interest:

- Glucose (hypoglycemia and hyperglycemia)
- Total bilirubin (blood bilirubin increased)
- ALP (alkaline phosphatase increased)
- AST (SGOT) (aspartate aminotransferase increased)
- ALT (SGPT) (alanine aminotransferase increased)
- INR (INR increased)
- Platelets (platelet count decreased)
- WBC/Leukocytes (white blood cell decreased and leukocytosis)
- Neutrophils (neutrophil count decreased)

10.7.2 Vital Signs

Vital signs will be summarized using descriptive statistics at each measurement time point. Systolic and diastolic blood pressure and heart rate will be summarized for each defined group using descriptive statistics at each scheduled visit. Apheresis subjects and non-apheresis subjects will be summarized in separate tables given different time points. Summaries will also include the change from baseline at each scheduled visit.

10.7.3 Electrocardiogram

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 group by scheduled visit. In each 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.

10.7.4 Anti-AMG 145 Antibodies

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

10.7.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the patient-month exposure to investigational product, the categorical representation of dose received, and the cumulative dose used by defined groups.

Exposure definitions are provided in Section 6.3.

11. Changes From Protocol-specified Analyses

The protocol specifies treatment-related adverse events will be tabulated by system organ class and preferred term for each treatment arm. This tabulation will not be included in the primary analysis. Instead treatment-related adverse events will be included in the overall adverse event summary and a tabulation of events of interest will be included.

12. Literature Citations / References

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13. Data not Covered by This Plan

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

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.

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 followings:

The record closest to the scheduled study day of the specific study week (7*study week+1) will be selected. 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.

Handling multiple records assigned to an analytical study week for apheresis patients:
For apheresis patients, their apheresis date is aligned with the scheduled visit. As such, when multiple records available during a visit window, the one on the same day as apheresis should be selected. If no apheresis record can be found during the visit window, then the records will be mapped using the target visit date instead. If both pre-and post-apheresis assessments were performed, the pre-apheresis assessment will be used for summary for the sake of this SAP.

Table A.1 Visit Windows for Labs, hsCRP, Antibodies and Vitamin E

Scheduled Visit Week	Scheduled Visit Study Day	Chemistry, Coagulation, Hematology, hsCRP, HbA1c	Anti-AMG 145 antibodies	Direct LDL, Direct VLDL	Fasting Vitamin E
Week 4	29			2-42	
Week 6	43				
Week 8	57			43-70	
Week 12	85	2-126	2-126	71-98	2-126
Week 16	113			99-126	
Week 20	141			127-154	
Week 24	169	127-210	127-210	155-210	127-210
Week 36	253	211-294	211-294	211-294	211-294
Week 48 / Year 1	337	295-378	295-504	>=295	295-420
Week 60	421	379-462			
Week 72	505	463-546			421-588
Week 84	589	547-630			
Week 96 / Year 2	673	631-714	505-882		>=589
…					
Week n	n*7+1	From (n-6)*7+1 to (n+6)*7			
Week 156 / Year 3	1093		883-1260		
Week 204 / Year 4	1429		1261-1638		
Week 264 / Year 5	1849		>=1639		

Where n = 108, 120, 132 and so on, incremental by 12, until 264

Table A.2 Visit Window for Vital Signs, Lipid Labs[a], Lp(a) PK and PCSK9

Scheduled Visit Week	Scheduled Visit Study Day	Vital Signs, Fasting plasma lipids[a], ApoA1, ApoB, Lp(a), PK, PCSK9		
		Parent Study Rollover	Non-Parent / Non-Apheresis	Non-Parent / Apheresis
Week 2	15			2-21
Week 4	29	2-35	2-35	22-35
Week 6	43	36-49	36-49	36-49
Week 8	57	50-70	50-70	50-60
Week 9	64			61-67
Week 10	71			68-77
Week 12	85	71-98	71-98	78-98
Week 16	113	99-126	99-126	99-126
Week 20	141	127-154	127-154	127-154
Week 24	169	155-210	155-210	155-210
…				
Week n	n*7+1	From (n-6)*7+1 to (n+6)*7	From (n-6)*7+1 to (n+6)*7	From (n-6)*7+1 to (n+6)*7

Where n=36, 48, 60 and so on, incremental by 12, until 264.
[a] Lipid panel excluding Direct VLDL and Direct LDL.

Table A.3 Visit Window for Endpoints Collected only at the End of Study

Scheduled Visit Week	Weight, Physical Exam, Urinalysis, 12 Lead ECG,eGFR
EOS	>1

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.