Statistical Analysis Plan

Protocol Title:	A Phase 1, Randomized, Double-blind, Placebo-controlled, Ascending Single Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 529 in Healthy Subjects
Short Protocol Title:	Phase 1 , Randomized, Double-blind, SAD study to Evaluate Safety, Tolerability, PK & PD of AMG 529
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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	adverse events
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ASGR1	asialoglycoprotein receptor, subunit 1
AST	aspartate aminotransferase
AUC_{inf}	area under the serum concentration-time curve from time 0 to infinity
BP	blood pressure
C_{max}	maximum observed concentration
CAD	coronary artery disease
CHD	coronary heart disease
CRF	case report form
CVD	cardiovascular disease
DILI	drug induced liver injury
DLRM	dose level review meeting
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FSH	follicle-stimulating hormone
GGT	gamma glutamyltransferase
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HepCAb	hepatitis C antibody
HDL-C	high-density lipoprotein
HIV	human immunodeficiency
HR	heart rate
IB	Investigator's brochure
ICF	informed consent form
IP	investigational product
IPIM	Investigational Product

Abbreviation or Term	Definition/Explanation
IV	Intravenous
LDL-C	low-density lipoprotein
MABEL	minimal anticipated biologic
NOAEL	no observed adverse
Mg	milligram
mL	milliliter
PD	pharmacodynamics
PK	pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
RR	Respiratory rate
SAE	serious adverse event
SAER	Serious Adverse Event Report
SC	subcutaneous
$t_{1/2}$	half-life
TBL	total bilirubin
TSH	thyroid stimulating hormone
ULN	upper limit of normal

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 1 for study 20160338, AMG 529 dated 1 May 2017. The scope of this plan includes the primary analysis (which is final analysis) planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of AMG 529 following single, ascending doses administered subcutaneously (SC) or intravenously (IV) in healthy subjects	• Subject incidence of treatment-emergent adverse events • Safety laboratory analytes, vital signs, and ECGs
Secondary	
• To characterize the pharmacokinetics (PK) of AMG 529 following single SC or IV dose administration in healthy subjects • To characterize the pharmacodynamic (PD) effects of AMG 529 on alkaline phosphatase (ALP) and lipids (ie, total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides)	• AMG 529 PK parameters including, but not limited to, maximum observed concentration (C_{max}), the time of maximum observed concentration (t_{max}), and area under the concentration-time curve (AUC) • Pharmacodynamic parameters: - ALP levels - Lipid Levels (ie, total cholesterol, LDL-C, HDL-C, and triglycerides)
Exploratory	
• To assess the effects of AMG 529 on potential biomarkers • To assess the effects of AMG 529 on alkaline phosphatase isoenzymes (eg, bone specific alkaline phosphatase and liver specific alkaline phosphatase) • To assess the effects of AMG 529 on apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) • To assess the immunogenicity of AMG 529 following single SC or IV dose administration, as necessary • To characterize the AMG 529 PK and PD relationship	• Measurements of potential biomarkers • Measurements of alkaline phosphatase isoenzymes • Measurements of ApoA1 and ApoB • Subject incidence of anti-AMG 529 antibodies, if measured • AMG 529 exposure (eg, dose, C_{max}, and/or AUC) and ALP change from baseline

2.2 Hypotheses and/or Estimations

- AMG 529 will be safe and well tolerated after single dose SC or IV administration in healthy subjects.
- AMG 529 PK profile following single dose SC administration will allow for determination of dose and frequency of administration in future multi-dose trials of AMG 529.

3. Study Overview

3.1 Study Design

This is a randomized, double-blind, placebo-controlled, ascending single-dose study in healthy subjects, which will be conducted at 1 to 3 sites in the United States.

Approximately 48 subjects will enroll in 1 of 6 dose cohorts (8 per cohort).

For cohorts 1, 2, 3, 4, and 5, eight (8) subjects will be randomized to receive AMG 529 or placebo SC in a 3:1 ratio at dose levels of 21, 70, 210, 420, and 700 mg, respectively.

In cohort 6, eight (8) subjects will receive AMG 529 or placebo IV in a 3:1 ratio at a dose level of 70 mg. The planned doses of AMG 529 are shown below:

Planned Treatment by Cohort

Cohort	Dose/Route	No. of Subjects		
		AMG 529	Placebo	Total
1	21 mg SC	6	2	8
2	70 mg SC	6	2	8
3	210 mg SC	6	2	8
4	420 mg SC	6	2	8
5	700 mg SC	6	2	8
6	70 mg IV	6	2	8

For all cohorts, the first 2 subjects (sentinel pair) will be randomized such that 1 subject will receive AMG 529 and 1 subject will receive placebo, and observed for at least 24 hours before the remaining subjects in the cohort are dosed, provided there are no safety or tolerability concerns as assessed by the principal investigator. Escalation to a higher dose cohort will only proceed when the previous dose regimen has been found to be safe and reasonably tolerated based on available safety and laboratory data through study day 15 for all subjects and upon unanimous decision at the Dose Level Review Meeting (DLRM). Enrollment can be initiated in cohort 5 and cohort 6 after the dose regimen in cohort 4 has been found to be safe and well tolerated. Cohort 6 will start enrollment after the completion of cohort 5 enrollment.

3.2 Sample Size

The sample size is based on practical considerations. Approximately 48 healthy subjects will enroll to participate in cohorts 1 through 6 of this study. With 6 subjects receiving AMG 529 in a cohort there is a 74% chance of detecting an adverse event with a true incidence of 20%. With 36 subjects receiving AMG 529 there is an 84% chance of detecting an adverse event with a true incidence of 5%.

4. Covariates and Subgroups

4.1 Planned Covariates

Baseline values may be used as a covariate in analyses. For any variable, unless otherwise defined, baseline is defined as the last assessment taken prior to the first administration of AMG 529 or placebo.

4.2 Subgroups

Not applicable.

5. Definitions

Age

Subject age at randomization will be determined using the age in years reported in the clinical database.

Baseline

For any variable, unless otherwise defined, baseline is the last assessment taken prior to the first investigational product administration.

ECG Analysis Value

On Day -1 baseline, three sets of triplicate ECGs will be collected ≥ 30 minutes apart and at other time-points single triplicate ECGs will be collected, approximately 60 seconds apart. The mean value of triplicate will be calculated and used in the analysis. If an ECG is missing within a triplicate, all available data will be averaged for that timepoint.

Baseline ECG

The baseline ECG is defined as the average of the mean of the triplicates at Day -1; the mean of values in a triplicate should be calculated before taking the mean of the triplicate averages.

Change from Baseline

Change from Baseline is the arithmetic difference between post-Baseline and Baseline.

End-of-Study

Primary Completion: the time when the last subject has completed the EOS visit as outlined in Section 7.1 of the Schedule of Assessments in the protocol.

End of Trial: the time when the last subject has completed either the EOS visit or the last safety follow-up visit.

The EOS for each cohort may be prolonged pending treatment- emergent data. Definitions of the end of study for an individual and completion of the study as a whole are detailed in Section 3.5.1 of the protocol.

Enrollment Date

Enrollment date is defined as the randomization date.

Investigational Product

The term 'investigational product' is used in reference to AMG 529 or placebo.

Study Day

Post study day 1: study day= (date - date of Study Day 1) + 1 Study Day

Pre study day 1: study day= (date – date of Study Day 1)

Study Day 1

Study day 1 is defined as the first day of administration of the investigational product after enrollment. The day prior to Study Day 1 is considered Day -1.

Treatment-Emergent Adverse Event (TEAE)

A treatment-emergent adverse event is any adverse event starting on or after the first dose of investigational product, as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events Summary CRF and up to end of study (EOS).

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: Fridericia-corrected QT Interval (QTcF)
$QTcF=QT/(RR/1000)^{1/3}$

6. Analysis Sets

For all analyses, subjects will be analyzed according to the dose and treatment they received, not the dose and treatment to which they were randomized.

6.1 Safety Analysis Set

The safety set will consist of all study subjects who receive at least one dose of AMG 529 or placebo.

6.2 Pharmacokinetic Analyses Set

The PK analysis set will consist of all subjects for whom at least one PK parameter or endpoint can be reliably estimated.

6.3 Pharmacodynamic Analyses Set

The PD analysis set will contain all study subjects who receive at least one dose of AMG 529 or placebo and for whom at least 1 PD parameter has a baseline and at least 1 post baseline measurement available.

7. Planned Analyses

The study will have dose level review meetings (DLRM) after each cohort. The DLRM members are responsible for dose level decisions. The key objectives of the DLRM are to review data, monitor safety, and make dose change decisions. The DLRM members will consist of the principal investigator or designee, Amgen Medical Monitor, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager or designee, and a Biostatistics representative or designee. Additional members may be added as needed (eg, PK scientist). DLRMs will be conducted blinded to the PI and the Clinical Research Manager or their designees.

7.1 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study. However study will have Dose Level Review Meetings (DLRMs) after each cohort.

7.1.1 Dose-cohort Study Escalations and Stopping Rules

Dose-Cohort Study Escalation

The DLRM members are responsible for dosing decisions, which may include escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing; or repetition or expansion of a cohort.

Study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events (including serious adverse events), electrocardiograms, vital signs, and safety laboratory results will be reviewed. If available, emerging PK and PD data may also be reviewed in a manner that does not unblind individual treatment assignments.

Dose Stopping and Review

Determination of the severity of adverse events will be as follows: grade 1 = mild (eg, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated, or does not interfere with activity); grade 2 = moderate (eg, minimal intervention indicated or interferes with activity); grade 3 = severe (eg, medically significant but not immediately life-threatening, prevents daily activity, or requires treatment); grade 4 = life-threatening (ie, refers to an event in which the subject was, in the view of the investigator, at risk of death at the time of the event); and grade 5 = fatal. Dosing will be stopped or modified by the DLRM members if suspected adverse drug reactions and/or changes in safety data (including but not limited to

vital signs, electrocardiogram (ECG), or clinical laboratory results) are observed and these changes pose a significant health risk. The unblinded Amgen Medical Monitor will review data in an unblinded manner on an ongoing basis, and may suspend dosing and convene a DLRM at any time based on emerging safety data. In addition, dose escalation will be stopped or modified as shown in table below.

Clinically or medically significant suspected adverse drug reactions, and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable.

Scenario	**Action**
Any occurrence of a Grade 2 suspected adverse drug reaction in 2 or more subjects in the same cohort	• Stop dosing additional subjects and convene DLRM (if event occurs outside of the regularly scheduled DLRM) • Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance • Consider unblinding as appropriate[1] • Upon unanimous decision by the DLRM members, one of the following decisions may be made: - stop enrollment of the cohort (if applicable) - resume enrollment of the cohort as planned - resume enrollment of the cohort at a lower dose - expand the cohort at same dose - add a lower dose cohort to the study - escalate to an intermediate dose (a dose lower than the next planned dose) - escalate to the next planned dose

Scenario	Action
Any occurrence of a Grade 3 or greater suspected adverse drug reaction	• Stop dosing additional subjects and convene DLRM (if event occurs outside of the regularly scheduled DLRM) • Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance • Consider unblinding as appropriate[1] • If the adverse event is determined by unanimous decision of the DLRM members to be related to study drug and clinically or medically significant, no further doses should be administered at this dose and no dose escalation should proceed. Enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study. • Otherwise, upon unanimous decision of the DLRM members, one of the following decisions may be made: - resume enrollment of the cohort as planned - resume enrollment of the cohort at a lower dose - expand the cohort at the same dose - add a lower dose cohort to the study - escalate to an intermediate dose (a dose lower than the next planned dose) - escalate to the next planned dose

[1] The Amgen Medical Monitor will be unblinded to treatment assignment throughout the duration of the study.
For other DLRM members, a subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject, or may impact the safety of subjects currently enrolled, or subjects in subsequent cohorts.

7.2 Primary Analysis

The primary analysis will occur after the database lock following last subject last visit.

7.3 Final Analysis

The primary analysis will be the final analysis.

8. Data Screening and Acceptance

8.1 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.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the rave database. The database will be subject to edit checks outlined in the Clinical Data Management Plan (DMP). See details of this section in the DMP.

8.3 Handling of Missing and Incomplete Data

The following imputation of missing values will be done:

- Incomplete adverse event and concomitant medication dates will be imputed as per Appendix A. If imputed dates are used, then they will be identified as such in the final study report.
- Laboratory measurements that are below the quantification limits will be considered equal to the lower limit of quantification for all analyses unless explicitly noted otherwise.
- Biomarker data that are below the quantification limits will be considered equal to half of the lower limit of quantification for all analyses unless specified otherwise.
- PK concentrations that are below the quantification limits will be set to zero when engaging non-compartmental model to compute PK parameters.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations. The clinical study team will identify and document the criteria for important protocol deviations following Amgen SOP.

8.5 Outliers

Details of detecting outliers can be found in the DMP or other data management document. In addition, outliers may be identified via the use of descriptive statistics. All confirmed outlier data will be included in the analyses presented in this statistical analysis plan unless there is sufficient scientific justification to exclude them.

Pharmacokinetic (PK) serum concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. Data distribution will be explored, if required, data transformations or alternative non-parametric methods of analyses will be utilized.

8.7 Validation of Statistical Analyses

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

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

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, and PD data. Data for subjects receiving placebo will be combined across all cohorts, except for adverse events where the combined SC cohorts will be summarized separately from the IV cohort. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be summarized by treatment group and at each time point when samples are collected. The number and percent of subjects reporting any treatment-emergent adverse events will be tabulated by system organ class and preferred term and will be further classified by relationship to treatment.

9.2 Subject Accountability

The number and percent of subjects who were enrolled, randomized, received investigational product, completed investigational product, discontinued from investigational product (including reasons for discontinuing),completed study, discontinued the study (including reasons for discontinuing) will be summarized by treatment group.

Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented. A subject listing and summary noting inclusion in each analysis subset will be reviewed for all subjects enrolled. A subject listing noting reason for discontinuation of treatment and reason for discontinuing the study will be reviewed.

A subject listing will be provided for randomization information, randomized treatment and actual treatments.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. 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. Eligibility deviations are defined in the protocol. The final IPD list is used to produce the list of subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided.

9.4 Demographic and Baseline Characteristics

Demographic (ie, age, age groups [< 65, >= 65 and >= 75], sex, race, ethnicity) and baseline characteristics (height, weight, body mass index) will be summarized by cohort and overall using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race as well as by the combination of race.

9.5 Efficacy Analyses

Not applicable.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

9.6.2 Adverse Events and Disease-related Events

All subjects who receive a dose of AMG 529 or placebo will be included in the safety analyses. Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term according to the medical dictionary for regulatory activities terminology. Tables of adverse events, fatal adverse events, and serious adverse events will also be provided if observed.

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or later will be used to code all adverse events to a system organ class and a preferred term. The subject incidence of adverse events by treatment group will be summarized for all treatment emergent, serious treatment emergent, treatment related, serious treatment related, those leading to withdrawal of investigational product, severe, life threatening and fatal adverse events.

The severity of each adverse event will be graded using protocol defined criteria. Subject incidence of treatment emergent events and treatment related treatment emergent events will further be summarized by worst severity grade. Subject incidence of all treatment emergent, serious treatment emergent, treatment emergent events leading to withdrawal of investigational product, and treatment emergent fatal adverse events will further be tabulated by system organ class and preferred term in descending order of frequency.

The above adverse event tables will not be created if two or fewer subjects in the study experience the adverse event. Narratives of any on-study deaths, serious treatment-emergent adverse events, including early withdrawals due to adverse events, also will be provided should they occur.

9.6.3 Laboratory Test Results

Summary statistics over time (for each protocol scheduled visit) by cohort for selected laboratory parameters (for Hematology and Clinical) as mentioned in below table. Additional summaries may include descriptive statistics of changes from baseline over time. For laboratory urinalysis parameters a separate subject listing will be reviewed.

Table of Selected Laboratory Parameters

Hematology	Clinical Chemistry	Urinalysis
Red Blood Cells	Albumin	Bilirubin
Hemoglobin	Glucose	Blood
Hematocrit	Calcium	Glucose
Mean Corpuscular Volume	Potassium	Ketones
Platelet count	Total CO2	pH
Mean Platelet Volume	Total bilirubin	Protein
White Blood Cells	Direct bilirubin	Specific Gravity
Total neutrophils	Alkaline phosphatase (ALP)	Urobilinogen
Eosinophils	Gamma-glutamyltransferase (GGT)	
Basophils	Estimated glomerular filtration rate (eGFR)	
Lymphocytes	Blood urea nitrogen (BUN)	
Monocytes	Chloride	
	Phosphorus	
	Magnesium	
	Creatinine	
	Creatine Kinase	
	Sodium	
	Total protein	
	Aspartate aminotransferase (AST)	
	Alanine aminotransferase (ALT)	

9.6.4 Vital Signs

Subject-level data for vital signs including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/min), and body temperature (C) will be presented and reviewed for each subject. The analyses of vital signs will include summary statistics over time (for each protocol scheduled study visit) by cohort. Depending on the size and scope of changes, summaries of changes from baseline over time may be provided.

9.6.5 Electrocardiogram

All on-study ECG data will be reviewed and may be plotted.

Each ECG will include the following measurements: QRS, QT, QTc, RR, and PR intervals. The Fridericia's (QTcF) QT correction will be computed as specified in section 5. All ECG parameters will be summarized over time and change from baseline over time will be provided. Further, subjects' maximum change from baseline in QTcF will be categorized in following categories and the number and percentage of subjects in each group will be summarized. Unscheduled assessments will be included in the determination of the maximum change.

- <= 30 msec
- > 30 – 60 msec
- > 60 msec

Subjects' maximum post baseline values in QTcF and QTcB will also be categorized in the following categories and the number and percentage of subjects in each group will be summarized.

- <= 450 msec
- > 450 – 480 msec
- > 480 – 500 msec
- > 500 msec

The number of subjects in each group will be summarized for each cohort. Baseline ECG recording is defined as the mean of the 3 sets of triplicate ECG results at study day 1 pre-dose (a total of 9 assessments).

9.6.6 Antibody Formation

If measured, anti-AMG 529 binding antibody will be assessed using a validated assay. The incidence of anti-AMG 529 antibodies will be listed for each subject. The number and percentage of subjects who develop anti-AMG 529 antibodies at any time, at baseline and during post-baseline visits may be summarized by cohort.

9.6.7 Exposure to Investigational Product

Descriptive statistics may be produced to describe the exposure to investigational product. Details for each AMG 529 administration will be reviewed for every subject. In addition, a listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

9.6.8 Exposure to Concomitant Medication

All medication will be coded using the WHO drug dictionary. Summary of concomitant medication use by preferred name will be provided.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

9.7.1.1 Analysis of Pharmacokinetic Endpoints

The Clinical Pharmacology Modeling and Simulation (CPMS) group at Amgen will perform this part of the analysis.

Serum samples will be analyzed for AMG 529 concentrations using a validated assay. Individual concentration-time plots for AMG 529 will be presented for each subject as well as mean concentration-time plots for each cohort. Pharmacokinetic parameters including but not limited to AUC, C_{max}, and t_{max} will be estimated using non-compartmental methods. Actual dosing and sampling times will be used for calculation of PK parameters.

Summary statistics will be generated for each PK parameter for each dose cohort. A population PK analysis may also be performed to obtain additional PK parameters. Bioavailability may also be calculated and summarized if data collected is deemed adequate.

9.7.1.2 Analysis of Pharmacodynamics Endpoints

Analyses of alkaline phosphatase (ALP) values will include summary statistics over time (for each protocol-scheduled visit) by cohort. Additional summaries may include descriptive statistics of change from baseline over time.

Analyses of lipids (total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides) will include summary statistics over time for each protocol-scheduled visit by cohort. Additional summaries may include descriptive statistics of changes from baseline over time.

An analysis of variance/covariance model will be applied to selected endpoints (ALP and Lipids levels) to evaluate the difference between treatment group and placebo over time. For this analyses the dependent continuous variable will be the endpoint response and independent variables will include subject, time, treatment group, and the interaction between time and treatment group. Both time and treatment will be considered nominal factors, and subject will be treated as a random factor. Baseline is included as a covariate in the model to adjust for baseline differences. A transformation to the data may be applied to attain homogenous variance and adjust for skewness prior to fitting the model. The data will be back transformed for result reporting. The treatment-by-time

longitudinal least square means will be estimated and reported with corresponding 95% confidence intervals.

9.7.2 Analyses of Biomarker Endpoints

Alkaline Phosphatase Isoenzymes

Analyses of alkaline phosphatase isoenzymes will include summary statistics over time (for each protocol scheduled visit) by cohort. Additional summaries may include descriptive statistics of changes from baseline over time.

Apolipoprotein A1 and Apolipoprotein B

Analyses of ApoA1 and ApoB will include summary statistics over time (for each protocol scheduled visit) by cohort. Additional summaries may include descriptive statistics of changes from baseline over time.

An analysis of variance/covariance model will be applied to selected end points (ALP Isoenzymes, Apolipoprotein A1 and Apolipoprotein B) to evaluate the difference between treatment group and placebo over time. For this analyses the dependent continuous variable will be the endpoint response and independent variables will include subject, time, treatment group, and the interaction between time and treatment group. Both time and treatment will be considered nominal factors, and subject will be treated as a random factor. Baseline is included as a covariate in the model to adjust for baseline differences. A transformation to the data may be applied to attain homogenous variance and adjust for skewness prior to fitting the model. The data will be back transformed for result reporting. The treatment-by-time longitudinal least square means will be estimated and reported with corresponding 95% confidence intervals.

10. Changes From Protocol-specified Analyses

There will be no changes to the protocol-specified analyses.

11. Literature Citations / References

AMG 529. Investigator's Brochure. Thousand Oaks, CA: Amgen Inc.

12. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

Imputation Rules for Partial or Missing Start Dates

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		
Start Date		<1st Dose	≥1st Dose	<1st Dose yyyymm	≥1st Dose yyyymm	<1st x`Dose yyyy	≥1st Dose yyyy	Missing
Partial: yyyymm	=1st Dose yyyymm	2	1	2	1	N/A	1	1
	≠ 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	=1st Dose yyyy	3	1	3	1	N/A	1	1
	≠ 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month. Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.