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

Amgen Protocol Number (AMG 529) 20160338

IND number BB-IND 132180

Clinical Study Sponsor: Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Tel: 805.447.1000

Key Sponsor Contact(s): PPD, MD
Medical Sciences Executive Medical Director
PPD

PPD
Clinical Research Study Manager
PPD

Date: 23 February 2017

Amendment 1 Date: 01 May 2017

Confidentiality Notice

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the institutional review board/independent ethics committee/institutional scientific review board or equivalent.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1- 800-77-AMGEN, Canadian sites, 1-866-50-AMGEN; Amgen's general number in the US (1-805-447-1000).

NCT Number: 03170193
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

Investigator's Agreement

I have read the attached protocol entitled 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, dated 01 May 2017, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 1

Indication: Coronary Artery Disease (CAD)

Primary Objective: To assess the safety and tolerability of AMG 529 following single, ascending doses administered subcutaneously (SC) or intravenously (IV) in healthy subjects

Secondary Objectives:

- 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)

Exploratory Objectives:

- 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

Hypotheses:

- 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.

Primary Endpoints:

- Subject incidence of treatment-emergent adverse events
- Safety laboratory analytes, vital signs, and ECGs

Secondary Endpoints:

- 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 Endpoints:

- 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

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.

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%.

Summary of Subject Eligibility Criteria:

Healthy women of non-reproductive potential and men ≥ 18 to ≤ 55 years of age at the time of randomization.

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2

Investigational Product

Amgen Investigational Product Dosage and Administration:

A total of 48 subjects will be randomized to receive 1 of 6 doses of AMG 529 or equivalent volume of placebo. Subjects will receive AMG 529 in fixed doses of 21, 70, 210, 420, or 700 mg SC, or 70 mg IV.

The planned dose escalation schedule may be modified based on treatment-emergent data (safety and/or PK). Dose adjustments (if any) will be made on a treatment cohort and not on an individual basis, and will be agreed upon by Amgen in coordination with the principal investigator.

Control Group: The control group will be those subjects who will be administered placebo. Within each cohort, 2 subjects will receive an equivalent volume of placebo.

Procedures:

Screening

After written informed consent has been obtained, all screening procedures and tests that establish study eligibility will be performed within 28 days prior to day 1 visit. Study procedures are summarized in the Schedule of Assessments.

Serious Adverse Events (SAEs) will be collected from the time the Informed Consent Form (ICF) is signed.

Day -1

Subjects will be admitted to the research facility the day before investigational product (IP) administration (day -1) and will reside at the facility until all assessments are completed on day 6. A subject will be considered enrolled once the subject is deemed eligible by the investigator based on screening and day -1 assessments.

Treatment

After completion of all pre-dose procedures on the day of dosing (day 1), subjects will receive AMG 529 or placebo. 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. Subjects will continue with the residency period through day 6, during which time blood and urine samples for laboratory assessments, PK, and PD measurements will be collected and safety assessments performed.

Upon discharge, subjects will return to the research facility on an outpatient basis at specified timepoints for the collection of blood and urine samples for laboratory assessments, PK and PD measurements, and completion of safety assessments through the end of the study.

All adverse events (including serious adverse events) and use of concomitant medication will be collected throughout the study.

End of Study (EOS)

Subjects in cohorts 1 (21 mg SC), 2 (70 mg SC) and 6 (70 mg IV) will return to the research facility for an end-of-study (EOS) visit on day 30. Subjects in cohorts 3 (210 mg SC), 4 (420 mg SC) and 5 (700 mg SC) will return to the research facility for an EOS visit on day 57. This visit will complete the subjects' participation in this study. If there is a clinically significant clinical or laboratory abnormality in need of monitoring, subjects will be followed until resolution of the abnormality or until it is considered stable.

Blood samples will be collected at baseline and EOS as outlined in the Schedule of Assessments for the measurement of anti-AMG 529 antibodies. The measurement of anti-AMG 529 antibodies will be conducted on these samples only if there are unexpected PK findings or a safety signal in this study or future studies that warrants further investigation by characterizing drug immunogenicity. Samples testing positive may be further characterized for quantity/titer, isotype, affinity, and/or in vitro neutralizing activity. If the anti-AMG 529 antibody samples are analyzed, subjects who test positive for binding antibodies at the final scheduled study visit and have clinical sequelae that are considered potentially related to an anti-AMG 529 antibody response may also

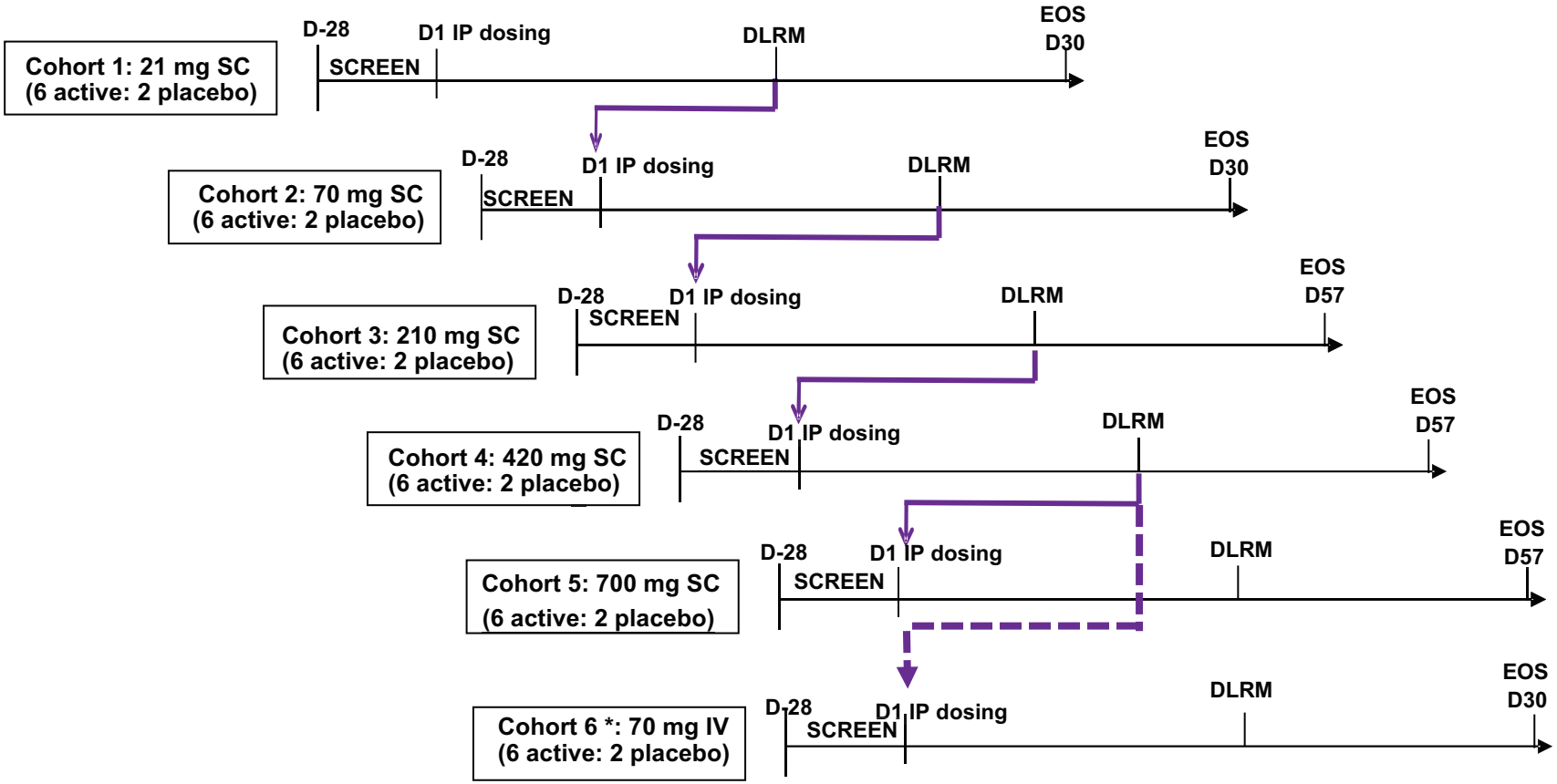
be asked to return for additional follow-up testing. This testing should occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks). More frequent testing (eg, every month), or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive AMG 529.

Statistical 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.

Sponsor: Amgen Inc.

Study Design and Treatment Schema



Cohorts will enroll sequentially after review of safety data up to day 15 at the previous dose level.
*Cohort 6 will open for enrollment immediately after cohort 5 is fully enrolled.

Study Glossary

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
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a study
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
Enrollment	defined as when the investigator has decided that the subject has met all eligibility criteria
EOS	end of study

Abbreviation or Term	Definition/Explanation
Exposure-Response Analysis	mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic [PK] exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic (PD) effects, efficacy and safety endpoints
FIH	first-in-human
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 cholesterol
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's brochure
ICF	informed consent form
INR	international normalized ratio
IP	investigational product
IPIM	Investigational Product Instruction Manual
IV	Intravenous
LDL-C	low-density lipoprotein cholesterol
MABEL	minimal anticipated biologic effect level
NOAEL	no observed adverse effect level
mg	milligram
mL	milliliter
PD	pharmacodynamics
PK	pharmacokinetics
Primary Completion	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
PT	prothrombin time
PTT	partial thromboplastin time
Randomization	defined as when a unique randomization number has been assigned to the subject
RR	respiratory rate
SAE	serious adverse event

Abbreviation or Term	Definition/Explanation
SAER	Serious Adverse Event Report
SC	subcutaneous
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
$t_{1/2}$	half-life
TBL	total bilirubin
TSH	thyroid stimulating hormone
ULN	upper limit of normal

TABLE OF CONTENTS

List of Tables

List of Figures

List of Appendices

1. OBJECTIVES

1.1 Primary

- To assess the safety and tolerability of AMG 529 following single, ascending doses administered subcutaneously (SC) or intravenously (IV) in healthy subjects

1.2 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)

1.3 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

2. BACKGROUND AND RATIONALE

2.1 Disease

Cardiovascular disease (CVD) is the leading cause of death globally (Word Health Organization, 2016). According to World Health Organization cardiovascular diseases fact sheet estimates, CVD accounted for 17.5 million deaths worldwide in 2012, approximately 31% of the total. Of the CVD related deaths, over 80% were due to coronary heart disease (CHD) and stroke (estimated at 7.4 million and 6.7 million deaths, respectively). It has been estimated that approximately one-half of all middle-aged men and one-third of all middle-aged women in the United States will develop CHD (Lloyd-Jones et al, 1999). There are approximately 15.5 million people with CHD in the United States, including 7.6 million with myocardial infarction and 8.2 million with angina pectoris (Mozaffarian et al, 2016b). Coronary heart disease is usually caused by the pathological process of atherosclerosis.

Treatment of CHD includes addressing the established risk factors with lipid lowering therapies, optimal management of diabetes, control of blood pressure and excess weight, and encouraging smoking cessation. Although meaningful progress in the control of established risk factors and the timely implementation of appropriate medical

and interventional/surgical therapies have contributed to the decline in mortality rates from CHD (Mensah et al, 2017), the burden of disease remains high. The facts below from the American Heart Association's Executive Summary: Heart Disease and Stroke Statistics - 2016 Update illustrate the magnitude of the problem in the United States (Mozaffarian et al, 2016a).

- CHD caused approximately 1 of every 7 deaths in the United States in 2013.
- CHD mortality was slightly more than 370,000 in 2013.
- It is estimated that each year 660,000 Americans will have a new acute coronary syndrome and 305,000 will have a recurrent episode. An additional 160,000 silent first myocardial infarctions are estimated to occur each year.
- Approximately, 1 American has a coronary event every 34 seconds and 1 American dies of one every 1 minute 24 seconds.

Therefore, despite the availability of medical and surgical interventions, there is an unmet medical need to further reduce the risk of CHD. Based on recent human genetic studies, AMG 529 is being developed to help address this unmet need.

2.2 Amgen Investigational Product Background

AMG 529 is a fully human monoclonal antibody that binds to the asialoglycoprotein receptor, subunit 1 (ASGR1) and blocks ligand binding. Recently, human genetic studies have identified a strong association between an *ASGR1* variant and CVD (Nioi et al, 2016). Icelandic heterozygous carriers of a rare 12-base-pair deletion (del12) loss-of-function variant in *ASGR1* had a lower level of non-high-density lipoprotein (HDL) cholesterol (-13.6 mg/dl; 95% CI, -17.7 to -9.4; $p=2.5x10^{-10}$), reduced risk for myocardial infarction (MI) (hazard ratio, 0.64; 95% CI, 0.64 to 0.80; $p=8.5x10^{-5}$) and coronary artery disease (CAD) (odds ratio 0.64; 95% CI, 0.51 to 0.80; $p=5.8x10^{-5}$), and increased lifespan compared to non-carriers (1.5 years; 95% CI, 0.2 to 2.8; p=0.02). The del12 variant was also associated with reduced levels of non-HDL cholesterol and risk of CAD in additional non-Icelandic populations. The reduced risk for CAD is larger than predicted based on the reduction of non-HDL cholesterol, suggesting possible beneficial cholesterol-independent effects yet to be determined.

ASGR1 encodes the major subunit of the hepatic asialoglycoprotein receptor (ASGPR), which is a hetero-oligomeric transmembrane protein consisting of two subunits, ASGR1 and ASGR2 (Weigel and Yik, 2002). ASGPR is expressed predominantly in liver parenchymal cells and is known to mediate the endocytosis and lysosomal degradation of asialoglycoproteins (desialylated glycoproteins; glycoproteins from which sialic acid has been removed). ASGPR binds to glycoproteins and other ligands that contain

terminal galactose or N-acetylgalactosamine residues. Numerous protein ligands have been proposed for ASGPR, including ALP (Hardonk and Scholtens, 1980), haptocorrin (a vitamin B12 transporter) (Burger et al, 1975), and asialofetuin (alpha-2-HS-glycoprotein) (Pricer and Ashwell, 1971).

Refer to the AMG 529 Investigator's Brochure (IB) for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.2.1 Pharmacology

AMG 529 binds to the carbohydrate-binding domain (CBD) of human ASGR1 and blocks ligand binding. AMG 529 cross-reacts to cynomolgus monkey and pig ASGR1, but does not show appreciable binding to dog, rat, or mouse ASGR1, or to human ASGR2. In vitro, AMG 529 binds to cells expressing recombinant human ASGR1 and blocks binding of the protein ligand asialofetuin. The binding affinity (K_D) of AMG 529 to human ASGR1 CBD recombinant protein is 34.5 pM and the IC_{50} is 25 nM in a cellular assay. In vivo, AMG 529 was pharmacologically active in cynomolgus monkeys as determined by a dose-dependent increases in serum ALP activity. Administration of multiple weekly doses of AMG 529 to diet-induced obese dyslipidemic cynomolgus monkeys resulted in prolonged elevation of ALP activity.

Refer to the AMG 529 IB for additional information related to pharmacology.

2.2.2 Pharmacokinetics

The PK of AMG 529 was characterized after single SC or IV bolus injection to cynomolgus monkeys. AMG 529 PK was non-linear over the dose range of 0.3 to 10 mg/kg SC. AMG 529 demonstrated rapid absorption with a mean t_{max} of approximately 1 day after SC administration. The mean terminal half-life ($t_{1/2,z}$) was approximately 7 days. The mean estimated bioavailability of AMG 529 after SC administration of 10 mg/kg was calculated to be 92%.

AMG 529 multiple-dose PK was characterized in cynomolgus monkey after 5, 20, or 100 mg/kg SC or 100 mg/kg IV of AMG 529 weekly for 2 weeks. AMG 529 exposure, as assessed by AUC_{last} and $C_{max,}$ increased greater than proportional to dose over the dose range of 5 to 100 mg/kg SC. The mean t_{max} occurred between 1.8 to 2.3 days. Modest accumulation (mean ratios ranged from 1.5 to 3.0) of AMG 529 upon weekly dosing was observed. The mean estimated bioavailability of AMG 529 after SC administration of 100 mg/kg was calculated to be 75%.

Refer to the AMG 529 IB for additional information related to pharmacokinetics.

2.2.3 Toxicology

A nonclinical toxicology program was conducted to support the AMG 529 single dose first-in-human (FIH) study. The Good Laboratory Practices (GLP) studies included a 14-day subcutaneous (SC) and intravenous (IV) repeat dose toxicology study conducted in cynomolgus monkeys, a 14-day repeat dose cardiovascular safety pharmacology study in telemeterized cynomolgus monkeys, and a tissue cross reactivity (TCR) study in a full panel of human tissues with fluorochrome-labeled AMG 529.

The toxicity profile of AMG 529 was characterized in the14-day repeat dose toxicology study in which AMG 529 was administered once weekly (for a total of 2 doses) at 5, 20, 100 mg/kg SC or 100 mg/kg IV. AMG 529 was well-tolerated in cynomolgus monkeys at all dose levels and the no observed adverse effect level (NOAEL) was 100 mg/kg given weekly by SC or IV administration.

All AMG 529-related changes were observed in select clinical pathology parameters consistent with intended pharmacology, ie, decreased clearance of serum glycoproteins due to AMG 529 inhibition of the ASGPR. Mildly to moderately increased serum ALP and minimally increased gamma glutamyltransferase (GGT) were observed at all dose levels. Both serum endpoints are reported ligands of ASGPR (Hardonk and Scholtens, 1980; Mortensen and Huseby, 1997). These changes had no corresponding clinical signs or changes in clinical pathology parameters suggestive of hepatocellular injury (ie, no increases in alanine transaminase [ALT] or aspartate transaminase [AST]), liver dysfunction (ie, no increases in total bilirubin, altered glucose, or prolonged prothrombin time [PT] or activated partial thromboplastin time [aPTT]), or gross or microscopic hepatobiliary or bone findings to suggest organ toxicity or injury.

A minimally shortened PT was identified in some male AMG 529-dosed cynomolgus monkeys in the repeat dose study at the 20 mg/kg SC and 100 mg/kg SC and IV dose levels. Coagulation proteins are also known ligands of ASGPR (Ellies et al, 2002; Bovenschen et al, 2005; Seested et al, 2010). The minimally shortened PT was considered non-adverse because of the low incidence, small magnitude of change, and lack of clinical signs or histopathological evidence of a thrombotic event in AMG 529-treated animals.

In a stand-alone, repeat-dose cardiovascular safety pharmacology study conducted in conscious telemeterized cynomolgus monkeys, there were no AMG 529 effects on electrocardiograms and hemodynamic parameters (including arterial blood pressure) at dose levels up to 100 mg/kg/dose-SC. Slight decreased appetite was noted in some

animals at 100 mg/kg, but was not considered adverse. The NOAEL on this study was considered to be 100 mg/kg SC.

In vitro binding of AMG 529 in the TCR study was observed only in the liver, specifically localized to the membrane and cytoplasm of hepatocytes.

Refer to the AMG 529 IB for additional information related to toxicology.

2.3 Risk Assessment

To date, AMG 529 has not been administered to human subjects; therefore, no clinical data are available. This is the first single dose study proposed in human subjects with AMG 529. The assessment of potential side effects of AMG 529 is based on the pre-clinical studies conducted to date (Section 2.2.3) and the literature.

In addition to the cardioprotective phenotype, the *ASGR1* del12 variant was associated with elevated levels of ALP (50.1% change; 95% CI, 42.9 to 57.2; $p=3.6x10^{-63}$) and vitamin B12 (16.6% change; 95% CI, 11.5 to 21.5; $p=3.1x10^{-12}$), proposed to result from reduced clearance by ASGPR (Nioi et al, 2016). Increased GGT (10.3% change; 95% CI 1.7 to 19.2; p=0.015) and decreased albumin (-0.72 g/L; 95% CI -1.37 to 0.06; p=0.033) were also observed, but did not reach genome-wide significance ($p=5x10^{-8}$). There was no association between the del12 variant and ALT (5.8% change; 95% CI -0.4 to 12.2; p= 0.065), AST (4.1% change; 95% CI -2.9 to 11.4; p=0.095), or bilirubin (3.7% change; 95% CI -2.6 to 10.4; p=0.25), suggesting that the increase in ALP was not likely due to underlying liver disease.

Increases in ALP and potentially GGT are expected with AMG 529 administration due to reduced clearance of these desialylated molecules from the circulation and are not indicative of hepatotoxicity. Alkaline phosphatase and GGT, along with other assessments of liver function (AST, ALT, bilirubin and albumin), will be monitored in this FIH study. The expectation is that only increases in ALP and potentially GGT will occur without clinically relevant increases in the other liver function tests.

Minimal reductions in PT were noted in the 14-day toxicology study in cynomolgus monkeys. While the clinical relevance of this finding is unclear, PT, international normalized ration (INR), and aPTT will be evaluated in all subjects.

As with any therapeutic antibody, administration of AMG 529 may result in systemic (eg, hypersensitivity) and local (eg, injection site) reactions, and immunogenicity (ie, the development of anti-AMG 529 antibodies). A sentinel dosing strategy will thus be used

for all cohorts of this study to mitigate the chances of subjects experiencing unexpected adverse events resulting from a single dose of AMG 529.

The proposed risk assessment and management plan for the study has been developed in accordance with the requirements of regulatory guidelines and strategies to identify and mitigate risks for FIH clinical trials with investigational medicinal products.

Refer to the AMG 529 IB, Section 7 for additional information related to potential side effects.

2.4 Rationale

Based on the genetic association of the *ASGR1* del12 variant with reduced risk of MI and CAD, and the stronger effect on CAD than predicted by its effect on non-HDL cholesterol levels alone, AMG 529 may reduce cardiovascular morbidity and mortality through both cholesterol-dependent and -independent effects. An FIH study is planned to investigate the effects of AMG 529 in humans.

2.5 Dose Rationale

This FIH study will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG 529. The selection of the dose range is based on safety margins established in the 14-day cynomolgus monkey toxicology study, the projected human exposures of AMG 529 obtained through analysis of cynomolgus monkey PK, and the projected changes in ALP in humans through analysis of the cynomolgus monkey AMG 529-ALP relationship based on PK and ALP data from cynomolgus monkeys following administration of AMG 529.

The starting dose of 21 mg administered SC for this FIH study was conservatively selected to be well below doses that may potentially be associated with toxicity. The proposed initial dose of AMG 529 for the FIH study was chosen in reference to the 100 mg/kg dose, which was the highest dose tested and the NOAEL determined from the 14-day GLP toxicity study in cynomolgus monkeys. Drug-related effects were consistent with the expected pharmacology of AMG 529. The animal model used (cynomolgus monkey) provides a highly relevant model for predicting human safety and pharmacodynamic assessments, since AMG 529 has similar affinity and activity at the cynomolgus monkey and human ASGPR. The anticipated half-life in humans is approximately 7-10 days.

Three approaches were used to assess the starting dose in this FIH study. The first approach was based on the Food and Drug Administration Guidance for Starting Dose

Estimation, "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers." The maximum recommended starting dose (MRSD) was calculated based on animal reference body weight and the formula for calculating human equivalent dose based on body surface area listed in the FDA guidance. Using a default safety factor of 10, the calculated MRSD in humans would be 225 mg (with body surface area correction) for a 70 kg individual based on the NOAEL in monkeys. The 21 mg starting dose (0.3 mg/kg) is approximately 1/10th of the estimated MRSD based on monkeys.

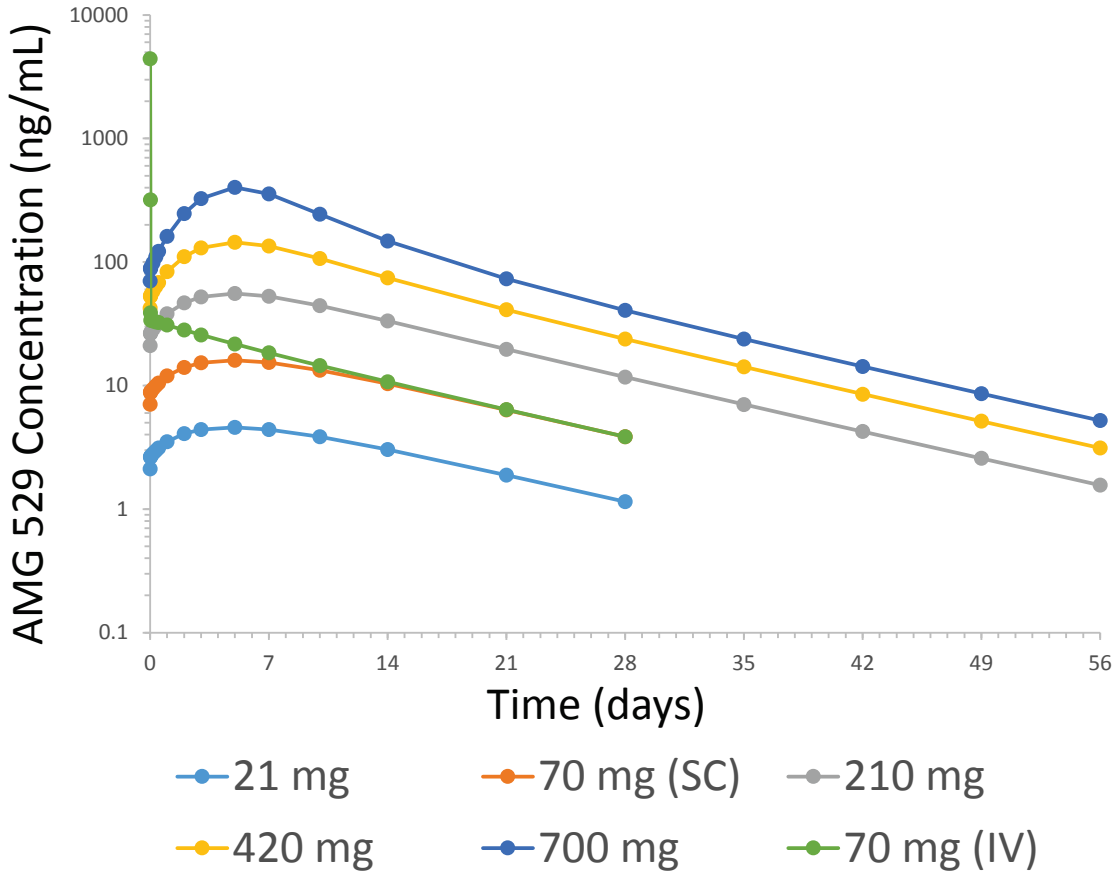
C_{max} and AUC-based safety margin determinations were the basis for the second approach (Table 1 and Figure 1). The NOAEL C_{max} and AUC are 479000-fold and 113000-fold higher than the predicted human C_{max} and AUC at the proposed starting dose of 21 mg SC in human subjects (ie, 4.59 ng/mL and 98.9 ng•day/mL). The anticipated maximum dose in the clinic, 700 mg SC, is expected to result in a C_{max} and AUC that are 5490-fold and 2060-fold lower, respectively, than those observed at the NOAEL dose in the 14-day GLP toxicology study, and is intended to provide adequate safety information supporting subsequent clinical development.

Table 1. Predicted AMG 529 Human Exposures After a Single Dose Administration for the Proposed Clinical Doses and Margins Relative to Repeat-dose Cynomolgus Monkey Exposure at the NOAEL

Clinical Dose (mg)	Predicted Human Exposure[a]		Exposure Margins[b]	
	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng•day/mL)	C_{max}	$AUC_{0\text{-}7d}$
21 SC	4.59	98.9	479000	113000
70 SC	16.0	337	138000	33200
210 SC	55.5	1090	39600	10300
420 SC	145	2510	15200	4460
700 SC	401	5450	5490	2060
70 IV	19400	468	113	23900

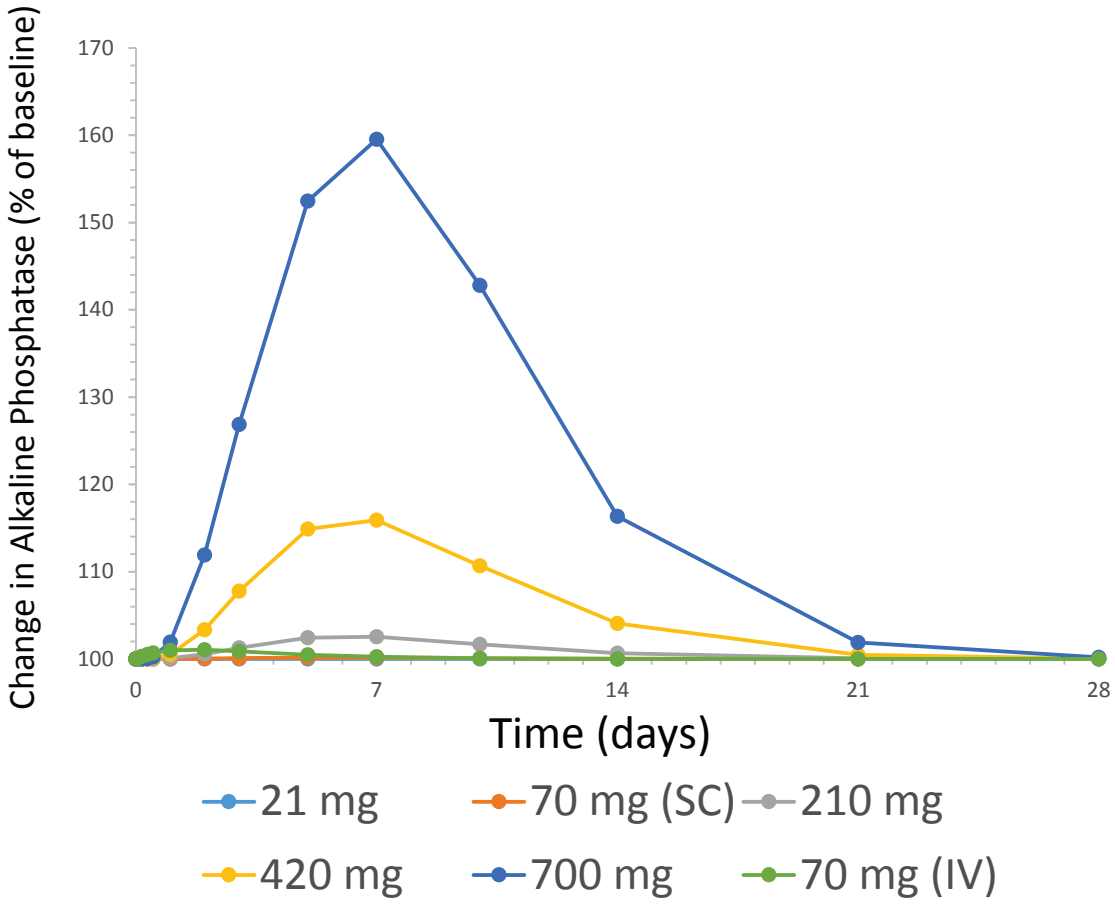
[a] Human exposures are the predicted human exposures assuming a single dose
[b] C_{max} of 2200 μg/mL and $AUC_{0\text{-}7d}$ of 11200 μg·day/mL at NOAEL (100 mg/kg SC) divided by predicted human exposure.
NOAEL= no observed adverse effect level; SC = subcutaneous; IV = intravenous; C_{max} = maximum observed concentration; $AUC_{0\text{-}inf}$ = area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-}7d}$ = area under the concentration-time curve from time 0 to 7 days after the 2nd dose

Figure 1. Predicted AMG 529 Concentration-time Profiles in Humans Following Single SC or IV Dose Administration of AMG 529



The third approach followed a 'Minimal Anticipated Biologic Effect Level' (MABEL) paradigm (EMEA/CHMP/SWP/28367/07, Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products). AMG 529 displayed a concentration dependent increase in ALP in cynomolgus monkeys with a maximum increase of 400% of baseline. The cynomolgus monkey PK-PD data were analyzed using an indirect response model and this model was utilized in conjunction with the predicted human exposure to estimate the increase in ALP in humans (Figure 2). The MABEL was defined as the dose that would result in a maximum of 10-15% increase in ALP from baseline. The predicted human exposures at a starting dose of 21 mg SC are anticipated to produce minimal to no change in ALP, much lower than a 10% increase from baseline. The highest proposed dose of 700 mg SC is anticipated to achieve a 1.6-fold increase from baseline in ALP demonstrating ASGR1 target engagement by AMG 529.

Figure 2. Predicted Alkaline Phosphatase Increase Relative to Baseline in Humans Following Single SC or IV Dose Administration of AMG 529



In summary, the dose range of 21 to 700 mg has a first dose which is 1/10th of the MRSD, is projected to result in human exposures lower than the exposures at the NOAEL or MABEL dose, is expected to provide an ample safety margin for subjects, and results in pharmacological activity useful for dose selection in subsequent clinical studies.

2.6 Clinical Hypotheses

AMG 529 will be safe and well tolerated after single dose SC or IV administration in healthy subjects. Additionally, 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. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 1, randomized, double-blind, placebo-controlled, ascending single-dose study in healthy subjects.

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.

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.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

This study will be conducted at 1-3 sites in the United States. Additional sites may be added as necessary to complete enrollment. Sites that do not enroll subjects within 1 month of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 48 healthy subjects will enroll in 1 of 6 cohorts. Each cohort will enroll 8 subjects.

3.4 Replacement of Subjects

In the event subjects are enrolled, but are withdrawn prior to IP administration, a replacement subject may be enrolled in the subject’s place and assigned to receive the identical treatment as the replaced subject. Additionally, subjects who are withdrawn from the study (see Section 8.3.2) may be replaced at the discretion of Amgen in consultation with the investigator or his or her designee. The replacement subject will be assigned to receive the identical treatment as the replaced subject.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

For cohorts 1 (21 mg SC), 2 (70 mg SC) and 6 (70 mg IV) subject participation will last up to approximately 58 days, including a 28 day screening period prior to protocol-required product administration and an on-study period lasting up to 30 days. For cohorts 3 (210 mg SC), 4 (420 mg SC) and 5 (700 mg SC) subject participation will last up to approximately 85 days, including a 28 day screening period prior to protocol-required product administration and an on-study period lasting up to 57 days.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoints, for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

101 Healthy men and women ≥ 18 to ≤ 55 years old with no history or evidence of clinically relevant medical disorders as determined by the investigator and the Amgen Medical Monitor if consulted

102 Body mass index (BMI) between 18 and 32 kg/m^2, inclusive, at screening

103 Women must be of non-reproductive potential:

- Postmenopausal defined as:
  - Age of 55 years with cessation of menses for 12 months or more, OR
  - Age < 55 years and no spontaneous menses for at least 12 months, AND with a follicle-stimulating hormone level > 40 IU/L or according to the definition of "postmenopausal range" for the laboratory involved; OR
- History of hysterectomy; OR
- History of bilateral oophorectomy

104 Men must agree to practice an acceptable method of effective birth control while on study through 90 days after receiving the dose of investigational product. Acceptable methods of effective birth control include sexual abstinence; vasectomy; or a condom with spermicide (men) in combination with barrier methods (diaphragm, cervical cap or cervical sponge), hormonal birth control or IUD (female partner of male participant).

105 Men must be willing to abstain from sperm donation while on study through 90 days after receiving the dose of investigational product.

4.2 Exclusion Criteria

201 Currently receiving treatment in another investigational device or drug study, or less than 30 days or 5 half-lives (whichever is longer), since ending treatment on another investigational device or drug study(s) prior to receiving the first dose of investigational product

202 Women who are lactating/breastfeeding or who plan to breastfeed while on study through 90 days after receiving the dose of investigational product

203 Men with partners who are pregnant or planning to become pregnant while the subject is on study through 90 days after receiving the dose of investigational product

204 Positive pregnancy test at screening or day -1

205 Estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2 as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at screening or day -1

206 Triglycerides ≥ 5.65 mmol/L (ie, 500 mg/dL) at screening

207 Gamma-glutamyltransferase (GGT) or ALP above the upper limit of normal (ULN) of the laboratory's reference range at screening or day -1. GGT or ALP may be retested once in case of an elevated GGT or ALP within 1.1 x ULN of the laboratory's reference range at screening or day -1.

208 ALT and AST > 1.1 upper limit of normal of the laboratory's reference range at screening or day -1

209 Prothrombin time or aPTT outside of the laboratory's normal reference range at screening or day -1

210 History of hyperthyroidism or hypothyroidism, unless treated and/or on stable therapy for > 6 months prior to enrollment, and confirmed by a thyroid stimulating hormone (TSH) level within the laboratory's normal reference range. Subjects with minor abnormalities in TSH may, at the principal investigator's discretion, be included if the subject is without clinical evidence of hyper- or hypothyroidism and additional thyroid function studies are within the laboratory's normal reference range.

211 History of malignancy of any type, other than in situ cervical cancer or surgically excised non-melanomatous skin cancers occurring more than 5 years prior to randomization

212 Positive results for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus ribonucleic acid (RNA). For hepatitis C, hepatitis C antibody (HepCAb) testing is done at screening, followed by hepatitis C virus RNA by polymerase chain reaction (PCR) if hepatitis C antibody is positive.

213 History or evidence of a clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen Medical Monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

214 Planned elective surgery to occur at any time from screening visit through EOS visit

215 Subject previously has entered this study

216 Use of any over-the-counter or prescription medications within the 14 days or 5 half-lives (whichever is longer), prior to dosing on day 1. Acetaminophen (up to 2 grams per day) for analgesia or hormone replacement therapy (eg, estrogen, thyroid) will be allowed if subject is stable on replacement therapy.

217 Use of any herbal medicines, vitamins or supplements known to affect lipid metabolism (eg, fish oils > 1000 mg/day, red yeast rice extract), within 30 days prior to dosing on day 1.

218 All herbal supplements, vitamins, and nutritional supplements (with the exception of those known to affect lipid metabolism, which are excluded as above) taken within 30 days prior to dosing on day 1 and continued use, if appropriate, must be reviewed and approved by the investigator and Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgement is required for subject participation.

219 History of substance abuse within 12 months before screening

220 Positive test for drugs of abuse or alcohol use at screening or on day -1

221 Subject has known sensitivity to any of the products or components to be administered during dosing.

222 Subject will not be available for protocol-required study visits or procedures (including the research facility residency period), to the best of the subject's and investigator's knowledge

223 Has donated or lost ≥ 500 mL of blood or plasma within 60 days of day 1

224 A corrected QT interval (QTcF) at screening of > 450 msec in men or > 470 msec in women or history of long QT syndrome

Systolic blood pressure ≥ 150 mm Hg or diastolic blood pressure ≥ 90 mm Hg at screening or day -1. For each visit, if the initial blood pressure is elevated, the reading may be repeated again at least 15 minutes later and the lower of the 2 readings may be used.

225 Subject is unwilling to refrain from strenuous exercise (eg, heavy lifting, weight training, and aerobics) for 72 hours prior to each blood collection for laboratory tests

226 Use of nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, pipes, or nicotine patches) during the 6 months before screening

227 Unwilling or unable to abstain from nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, pipes, or nicotine patches) throughout the course of the study

228 Subject is unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol is prohibited 48 hours prior to admission to the research facility (day -1) and throughout the residency period and is limited to no more than 2 drinks per day for the duration of the study (1 drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine or 1.5 ounces of 80 proof distilled spirits).

229 Any other condition that might reduce the chance of obtaining data required by the protocol (eg, known poor compliance) or that might compromise the ability to give truly informed consent

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the ICF before commencement of study-specific activities/procedures.

Each subject who enters into the screening period for the study (defined as the time at which the subject signs the informed consent) will receive a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. Re-screening of subjects is acceptable upon discussion with and approval by the Amgen Medical Monitor.

PPD [redacted]

A subject is considered enrolled when the investigator has decided that the subject has met all eligibility criteria. After a subject is considered enrolled, a randomization number is assigned. The investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

5.1 Randomization/Treatment Assignment

On day -1, eligible subjects will be randomized to a treatment assignment in a double-blind fashion. Within each cohort, subjects will be randomly assigned in a 3:1 ratio to receive either AMG 529 or placebo. They will be assigned a randomization number based in sequential order in which they qualified to be randomized. Subjects will be considered randomized once a unique subject randomization number has been assigned. Dosing should occur within 1 day of randomization. The randomization date is to be documented in the subject's medical record and on the enrollment case report form (CRF). 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.

A randomization schedule, based on a computer-generated randomization list prepared by Amgen, will be provided to the unblinded pharmacist at the site. The unblinded pharmacist will prepare all treatments accordingly and will randomize all subjects based on the randomization schedule.

5.2 Site Personnel Access to Individual Treatment Assignments

The subjects and the investigative staff, except for the unblinded pharmacist, will be blinded to treatment assignment. A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of subjects currently enrolled or subjects in subsequent cohorts. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged

to contact the Amgen Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

Treatment assignments will be unblinded after initial database lock. After initial database lock and receipt of written authorization from Amgen to unblind, the unblinded pharmacist will release the specified unblinded pharmacy records to site staff designated to enter the subject treatment into each subject's Unblinded Investigational Product Administration Case Report Form (CRF).

6. TREATMENT PROCEDURES

6.1 Classification of Products

The Amgen Investigational Product and/or placebo used in this study include: AMG 529 and placebo.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 529 and placebo.

6.2 Investigational Product

All investigational product will be administered at the research facility by a qualified staff member.

A physician must be available at the time of administration of Investigational Product.

6.2.1 Amgen Investigational Product AMG 529 and Placebo

AMG 529 for SC and IV administration will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. AMG 529 is provided in 5 mL sterile vials filled with a 1 mL deliverable volume of 70 mg/mL AMG 529. Placebo will be presented in identical containers and stored/packaged the same as AMG 529.

6.2.1.1 Dosage, Administration, and Schedule

The planned doses of AMG 529 are shown in Table 2. Doses will be administered on Day 1 following all required pre-dose procedures. All cohorts will be dosed in a staggered fashion where 2 subjects will be dosed (randomized to AMG 529 or placebo in a 1:1 ratio), followed by the remaining 6 subjects separated by at least 24 hours, provided there are no safety or tolerability concerns as assessed by the principal investigator.

Table 2. 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

The dosing schedule is described by a schema in the protocol synopsis.

The date, time, package lot number, and quantity administered are to be recorded on the individual subject's Investigational Product Administration CRF prior to database lock.

The effects of overdose of this product are not known.

6.2.1.2 Dose-cohort Study Escalation and Stopping Rules

6.2.1.2.1 Dose Level Review Meetings

Dose Level Review Meetings will be held to review data, monitor safety and make dose change decisions. The Dose Level Review Meeting (DLRM) members will be composed of the principal investigator or designee, the unblinded Amgen Medical Monitor, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager or designee, and biostatistics representative or designee. Additional members may be added as needed (eg, clinical pharmacology scientist). The DLRM voting members include the principal investigator or designee, Amgen Medical Monitor and Amgen Global Safety Officer or designee.

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. The data to be reviewed may not have been monitored or queried.

Except for the unblinded Amgen Medical Monitor who will review data on an ongoing basis throughout the duration of study in an unblinded manner, data will be reviewed by the rest of the DLRM members in a blinded manner (ie, treatment assignment will not be revealed) unless unblinding is deemed necessary for the review team to make dosing decisions. Unblinding can be performed at any time by the investigator or Amgen if deemed necessary for subject safety. If deemed necessary, unblinding will be performed according to Amgen standard procedures.

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 study data through study day 15 for all subjects and upon unanimous decision of the DLRM members. Available data from previous cohorts will also be considered. The next cohort will be open for enrollment immediately following the DLRM decision. 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.

The planned dose escalation schedule may be modified based on treatment-emergent data (safety and/or PK). Dose adjustments, if any, will be made on a treatment cohort and not on an individual basis, and will be agreed upon by Amgen in coordination with the principal investigator.

The review of available safety data and dosing change decisions will be documented in meeting minutes. Amgen will issue a written notification of the dose change decision to investigators.

6.2.1.2.2 Dose Stopping Rules

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 3.

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.

Table 3. Cohort Dose Stopping Rules

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 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

Page 1 of 2

Footnotes defined on next page of the table

Table 3. Cohort Dose Stopping Rules

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: o resume enrollment of the cohort as planned o resume enrollment of the cohort at a lower dose o expand the cohort at the same dose o add a lower dose cohort to the study o escalate to an intermediate dose (a dose lower than the next planned dose) o escalate to the next planned dose

Page 2 of 2

[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.

6.3 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio [INR] and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies as specified in the

FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.3.1 Criteria for Permanent Withholding of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Following the single-dose administration of study drug, the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2x upper limit of normal (ULN) or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	≥ 3x ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
  - Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-one antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
  - Non-hepatic causes (eg, rhabdomylosis, hemolysis)

6.4 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.8.

Concomitant therapies are to be collected from informed consent through EOS. Therapy name, indication, dose, unit, frequency, route, start date and stop date should be collected.

Acetaminophen (up to 2 grams per day) for analgesia, or hormone replacement therapy (eg, estrogen, thyroid) will be allowed if subject is stable on replacement therapy. Any herbal medicines, vitamins and supplements consumed by the subject within 30 days prior to receiving the first dose of AMG 529 and continuing use if considered appropriate, will be reviewed by the principal investigator and Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgment are required for subject participation. Details of all concomitant medications will be recorded in the subject's source documents and on the CRF.

6.5 Alcohol and Tobacco Restrictions

Subjects must limit alcohol consumption throughout the course of the study. Alcohol is prohibited 48 hours prior to admission to the research facility (day -1) and throughout the residency period and is limited to no more than 2 drinks per day for the duration of the study (1 drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine or 1.5 ounces of 80 proof distilled spirits).

Only non-nicotine or tobacco using subjects should be enrolled. Subjects should not have used any nicotine or tobacco containing products within the last 6 months prior to screening. Subjects must abstain from nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, pipes, or nicotine patches) throughout the screening period and for the duration of the study.

6.6 Exercise Restrictions

Subjects are required to refrain from strenuous exercise (eg, heavy lifting, weight training, and aerobics) for 72 hours prior to each blood collection for laboratory tests for the duration of the study. Walking at a normal pace will be permitted.

6.7 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s), device(s), or combination product(s) provisioned

and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.8 Excluded Treatments, Medical Device Use, and/or Procedures During Study Period

With exception to acetaminophen up to 2 g per day for analgesia and hormone replacement therapy (eg, estrogen, thyroid), use of any over-the-counter or prescription medications within the 14 days or 5 half-lives (whichever is longer) prior to dosing on day 1 and for the duration of the study is not permitted unless to treat a medical emergency. Additionally, use of any herbal medicines, vitamins or supplements known to affect lipid metabolism (eg, fish oils > 1000 mg/day, red yeast rice extract), within 30 days prior to dosing on day 1 and for the duration of the study is not permitted. It is also recommended that subjects avoid starting new or changing herbal medicines, vitamins and supplements reviewed and approved by the principal investigator and Amgen Medical Monitor during the study. Any changes regarding concomitant medications should be recorded on the subject's source documents and the CRF along with the reason for the change.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 4. Schedule of Assessments for Cohorts 1, 2, and 6

Activity	Screening		Treatment															EOS
Study Day	(-28 to -2)	-1	1						2		3	4	6	8	11	15	22	30
Time (in hours) [a]			Pre-Dose	0	0.5	1	6	12	24	36	48	72	120	168	240	336	504	696
Informed Consent	X																	
In-House Residency		X<											>X					
Medical History	X	X																
Body Weight	X																	X
Body Mass Index	X																	
Height	X																	
Vital Signs (HR, RR, BP, TEMP)	X	X	X			X [c]	X	X	X		X	X	X	X	X	X	X	X
Physical Examination	X	X																X
12-lead ECG [b]	X		X			X [c]	X	X	X		X	X	X	X	X	X	X	X
eGFR	X	X																X
Clinical Chemistry [d]	X	X							X		X [e]	X	X [e]	X [e]	X	X [e]	X	X
Clinical Hematology	X	X							X			X			X		X	X
PT/INR and aPTT	X	X							X			X			X		X	X
Urinalysis	X	X							X			X			X		X	X
Screening Lipid Panel [d]	X																	
On-study Lipid Panel [d]			X								X		X		X		X	X
Drug and Alcohol Screen	X	X																
HIV, HBsAg, HBcAb, HepCAb [f]	X																	
Pregnancy Test (females only)	X	X																X
Serum FSH Test (females only) [g]	X																	
Randomization		X																
Study Drug Administration				X														
Anti-Drug Antibody Sample Collection			X															X
PK Sample Collection (SC cohorts only)			X [h]				X	X	X	X	X	X	X	X	X	X	X	X
PK Sample Collection (IV cohort only)			X [h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alkaline phosphatase isoenzymes			X								X			X				X
Collect blood for biomarker development [i]			X								X			X				X
Pharmacogenetic (optional) [j]			X															
Adverse Event Recording				X<														>X
Serious Adverse Event Recording	X<																	>X
Concomitant Medications	X<																	>X

[a] Time in hours are relative to IP administration
[b] A single ECG will be collected at screening. Prior to dosing day 1, 3 baseline ECGs will be collected approximately 30 minutes apart. Each baseline ECG will be in triplicate to be collected 30 seconds apart for a total of 9 ECGs. Triplicate ECGs, to be collected 30 seconds apart, will be collected at all timepoints after dosing on day 1.
[c] For IV cohort only
[d] 10 hour fasting is required at all time points
[e] Alkaline phosphatase only on days 3, 6, 8, and 15
[f] If the results show a positive HepCAb: hepatitis C virus RNA by PCR is necessary.The test must be confirmed negative at screening for the subject to be eligible for study.
[g] Serum FSH Test (females only) for postmenopausal status will be conducted as per Section 7
[h] Pre-dose PK sample will be collected approximately 1 hour prior to dosing
i Biomarker samples (plasma and serum) to be collected on days 1, 3, 8, and 30
[j] Pharmacogentic sample obtained from cell pellet from the biomarker plasma sample collection at pre-dose (day 1) only

Table 5. Schedule of Assessments for Cohorts 3, 4, and 5

Activity	Screening		Treatment																EOS
Study Day	(-28 to -2)	-1	1				2		3	4	6	8	11	15	22	30	43		57
Time (in hours) [a]			Pre-Dose	0	6	12	24	36	48	72	120	168	240	336	504	696	1008		1344
Informed Consent	X																		
In-House Residency		X<																	>X
Medical History	X	X																	
Body Weight	X																		X
Body Mass Index	X																		
Height	X																		
Vital Signs (HR, RR, BP, TEMP)	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X		X
Physical Examination	X	X														X			X
12-lead ECG [b]	X		X		X	X	X		X	X	X	X	X	X	X	X	X		X
eGFR	X	X																	X
Clinical Chemistry [c]	X	X					X		X [d]	X	X [d]	X [d]	X	X [d]	X	X	X [d]		X
Clinical Hematology	X	X					X			X			X		X	X			X
PT/INR and aPTT	X	X					X			X			X		X	X			X
Urinalysis	X	X					X			X			X		X	X			X
Screening Lipid Panel [c]	X																		
On-study Lipid Panel [c]			X						X		X		X		X	X			X
Drug and Alcohol Screen	X	X																	
HIV, HBsAg, HBcAb, HepCAb [e]	X																		
Pregnancy Test (females only)	X	X																	X
Serum FSH Test (females only) [f]	X																		
Randomization		X																	
Study Drug Administration				X															
Anti-Drug Antibody Sample Collection			X																X
PK Sample Collection			X [g]		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Alkaline phosphatase isoenzymes			X						X			X				X			
Collect blood for biomarker development [h]			X						X			X				X			
Pharmacogenetic (optional) [i]			X																
Adverse Event Recording				X	<														>X
Serious Adverse Event Recording	X<																		>X
Concomitant Medications	X<																		>X

[a] Time in hours are relative to IP administration
[b] A single ECG will be collected at screening. Prior to dosing day 1, 3 baseline ECGs will be collected approximately 30 minutes apart. Each baseline ECG will be in triplicate to be collected 30 seconds apart for a total of 9 ECGs. Triplicate ECGs, to be collected 30 seconds apart, will be collected at all timepoints after dosing on day 1.
[c] 10 hour fasting is required at all time points
[d] Alkaline phosphatase only on days 3, 6, 8,15, and 43
[e] If the results show a positive HepCAb: hepatitis C virus RNA by PCR is necessary. The test must be confirmed negative at screening for the subject to be eligible for this study.
[f] Serum FSH Test (females only) for postmenopausal status will be conducted as per Section 7
[g] Pre-dose PK sample will be collected approximately 1 hour prior to dosing
[h] Biomarker samples (plasma and serum) to be collected on days 1, 3, 8, and 30
[i] Pharmacogentic sample obtained from cell pellet from the biomarker plasma sample collection at pre-dose (day 1) only

Refer to the applicable supplemental laboratory and ECG manuals for detailed collection and handling procedures.

7.2 General Study Procedures

Before any study-related screening or baseline procedure can be completed, a subject must sign and date the IRB-approved ICF. Every effort should be made to conduct study procedures as described in the scheduled Schedule of Assessments (Table 4 and Table 5). Any missed visits, tests not done, and examinations not conducted must be reported as such on the CRFs. Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the investigator's discretion. In the event that multiple procedures are required to be conducted at the same time, ECG and vital sign assessments should be performed before blood samples are drawn.

Blood draws and safety assessments on day 1 should be performed before IP administration. Every effort should be made to perform study procedures as scheduled.

Acceptable deviation windows are as follows:

- ± 10 minutes on day 1
- ± 1 hour on days 2-6
- ± 1 day on days 8-22
- + 3 days on day 30
- ± 3 days on days 43 and 57

Laboratory samples will be analyzed as follows:

- Hematology, chemistry, alkaline phosphatase isoenzymes, urinalysis, serology, screening lipid panel, coagulation assessments, and serum pregnancy test will be analyzed at local laboratories.
- PK, biomarker development, and anti-AMG 529 antibody samples will be sent to Amgen or its designee, for analysis (if applicable) and storage.
- The on-study lipid panel will be analyzed at a central laboratory.

Refer to the provided Amgen manual for detailed collection, processing, and shipping procedures.

7.2.1 Screening

After informed consent is obtained, screening procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 4 and Table 5).

Rescreen Subjects: A new (ICF) must be signed unless it has been < 28 days since the previous ICF signature was obtained.

Repeat Assessments: Screening assessments (eg, vital signs, ECGs, laboratory assessments, and urine drug screen) may be repeated during screening. The decision to re-screen a subject will be made on a case-by-case basis at the discretion of the Principal Investigator in consultation with the Amgen Medical Monitor. The decision regarding whether a subject has failed screening after repeat assessment will be decided on a case-by-case basis at the discretion of the Principal Investigator.

The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 4 and Table 5).

- Confirmation that the ICF has been signed
- Demographic data including sex, age, race, and ethnicity will be collected
- Physical Examination as per standard of care
- Medical/surgical history
- Height, weight and BMI
- Vital signs (eg, blood pressure, respiratory rate, heart rate, oral temperature)
- 12 lead ECG
- eGFR
- Safety laboratory assessments including clinical chemistry, hematology, coagulation, urinalysis, urine drug and alcohol screening, HIV antibodies, HBsAg, HBcAb, HepCAb, and serum pregnancy and FSH test (female subjects only)
- Screening lipid panel
- Serious Adverse Event reporting from the time the ICF is signed
- Documentation of all concomitant medications

7.2.2 Day -1

The following procedures are to be completed on day -1 as described in the Schedule of Assessments (Table 4 and Table 5).

- Physical examination
- Vital signs (blood pressure, respiratory rate, heart rate, and oral temperature)
- Update to medical/surgical history as applicable
- Safety laboratory assessments: clinical chemistry, hematology, coagulation, urinalysis, urine drug and alcohol screening, pregnancy test (female subjects)
- eGFR
- SAE reporting
- Randomization

- Documentation of all concomitant medications
- In-house residency per Schedule of Assessments

7.2.3 Treatment

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 4 and Table 5).

- IP administration on day 1
- Vital signs (eg, blood pressure, respiratory rate, heart rate, oral temperature)
- Triplicate 12-lead ECG
- Safety laboratory assessments: clinical chemistry, hematology, coagulation, and urinalysis
- Physical examination (cohorts 3, 4 and 5)
- On-study lipid panel
- PK, anti-AMG 529 antibody, biomarker, alkaline phosphatase isoenzymes, and pharmacogenetics sample collection
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of all concomitant medications
- In-house residency per Schedule of Assessments

7.2.4 End of Study Visit

Subjects will return to the clinic for follow-up visits in accordance to the Schedule of Assessments (Table 4 and Table 5) and be followed through the completion of the EOS procedures on day 30 for cohorts 1 (21 mg SC), 2 (70 mg SC) and 6 (70 mg IV) and day 57 for cohorts 3 (210 mg SC), 4 (420 mg SC) and 5 (700 mg SC). If an EOS test result demonstrates a clinically significant clinical or laboratory abnormality, the subject will be followed until resolution of the abnormality or until it is considered clinically stable by the investigator.

At the EOS visit, the following measures will be performed as per the Schedule of Assessments:

- Physical Examination
- Weight
- Triplicate 12-lead ECG
- Vital signs (eg, blood pressure, respiratory rate, heart rate, oral temperature)
- Safety laboratory assessments: clinical chemistry, hematology, coagulation, and urinalysis
- eGFR

- On-study lipid panel
- PK, biomarker (only for cohorts 1, 2 and 6), alkaline phosphatase isoenzymes (only for cohorts 1, 2 and 6) and anti-AMG 529 antibody sample collection
- Pregnancy test (female subjects only)
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of all concomitant medications

7.2.5 Description of Study Procedures

7.2.5.1 Informed Consent

After informed consent has been obtained, all screening procedures and tests establishing eligibility will be performed within 28 days of day 1. Screening procedures are summarized in the Schedule of Assessments (Table 4 and Table 5).

7.2.5.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety.

7.2.5.3 Subject Residency

Eligible subjects will be checked into the clinical site on day - 1 and will be discharged after all assessments and procedures are completed at the end of day 6.

7.2.5.4 Meal and Hydration Requirements

Subjects will be required to fast overnight for at least 10 hours prior to blood draws per the Schedule of Assessments in Table 4 and Table 5.

7.2.5.5 Medical History

A complete medical history will be obtained at screening by the investigator or designated site physician. Medical history will include information on the subject's current health and surgical history. Relevant medical history findings will be recorded in the subject's source and on the appropriate pages of the CRF. Any unresolved medical history will be graded 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.

7.2.5.6 Physical Examination

The investigator or designated site physician will perform a complete physical examination (excluding breast, genital, and rectal examination) at time points specified in the Schedule of Assessments (Table 4 and Table 5). Predose abnormal findings will be reported on the medical history page of the CRF.

7.2.5.7 Vital Signs

Vitals signs (blood pressure, respiratory rate, heart rate, and oral temperature) will be recorded by the investigator or designee at time points specified in the Schedule of Assessments (Table 4 and Table 5). Subjects must be seated or in a semi-fowlers position for at least 5 minutes prior to vital signs measurements. The position and temperature location selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Abnormal measurements may be repeated at the discretion of the investigator and must be reported on the corresponding CRF page.

7.2.5.8 Electrocardiogram

Electrocardiogram (ECG) will be performed using standard ECG machine at time points specified in the Schedule of Assessments (Table 4 and Table 5). Subject must be in a semi-Fowler position in a rested and calm state for at least 5 minutes before the ECG assessment is conducted. If the subject is unable to be in the semi-Fowler, the subject should be in the most recumbent position possible. The ECG must include the following measurements: RR, QRS, QT, QTc, and PR intervals.

With the exception of the Screening ECG, which will be performed as a single ECG, all ECGs should be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures.

On day 1 pre-dose ECGs will be performed on 3 occasions separated by at least 30 minutes all in triplicate for a total of 9 ECGs (3 sets of triplicate).

At all other time points, ECGs will be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures.

The investigator will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

7.2.5.9 Height Measurement

Height measurement (in centimeters and without shoes) will be obtained at time points specified in the Schedule of Assessments (Table 4 and Table 5).

7.2.5.10 Body Weight

Weight measurement (in kg and without shoes) will be obtained at time points specified in the Schedule of Assessments (Table 4 and Table 5).

7.2.5.11 Body Mass Index

Body mass index will be calculated from the height and weight measurements obtained at screening as follows, BMI (kg/m^2) = weight (kg) / (height [cm]/100)^2.

7.2.5.12 Concomitant Medications

Concomitant medication(s) will be recorded throughout the study in the source documents and CRF. Sites will collect therapy name, indication, dose, unit, frequency, route, and start and stop dates for all concomitant medications.

7.2.5.13 Adverse Events/Serious Adverse Events

Adverse event and serious adverse event assessments will be made as specified in the Schedule of Assessments (Table 4 and Table 5) and will be evaluated and recorded in the source documents and on the CRF as specified in Section 9. Determination of the severity of all adverse events will be consistent with the Adverse Event Grading Scale Appendix A unless specified otherwise.

7.2.5.14 Clinical Laboratory Assessments

Blood will be collected after fasting at least 10 hours at all clinical chemistry time points.

All local laboratory tests must be reviewed and signed by the Principal Investigator or qualified designee. Additional safety laboratory assessments may be performed if clinically indicated.

The following laboratory tests will be conducted on samples collected and analyzed by standard laboratory procedures:

7.2.5.14.1 Hematology

The following hematology tests listed below will be performed:

Table 6. Hematology Panel

Red Blood Cells Hemoglobin Hematocrit Mean Corpuscular Volume Platelet count Mean Platelet Volume	White Blood Cells • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes

7.2.5.14.2 Coagulation Tests

The following coagulation tests will be performed: prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). The unblinded Amgen Medical Monitor will obtain, as necessary, consultation with a hematologist for changes in coagulation tests.

7.2.5.14.3 Clinical Chemistry

The clinical chemistry tests listed below will be performed:

Table 7. Clinical Chemistry Panel

Albumin	Blood urea nitrogen (BUN)
Glucose	Chloride
Calcium	Phosphorus
Potassium	Magnesium
Total CO_2	Creatinine
Total bilirubin	Creatine Kinase
Direct bilirubin	Sodium
Alkaline phosphatase (ALP)	Total protein
Gamma-glutamyltransferase (GGT)	Aspartate aminotransferase (AST)
Estimated glomerular filtration rate (eGFR) reported by the local laboratory	Alanine aminotransferase (ALT)

7.2.5.14.4 Urinalysis

The urinalysis tests listed below will be performed:

Table 8. Urinalysis

Bilirubin	Microscopic Exam*
Blood	• White blood cells
Glucose	• Red blood cells
Ketones	• Epithelial Cells
pH	• Casts
Protein	• Bacteria
Specific Gravity	• Crystals
Urobilinogen	

* Performed at the discretion of the PI or qualified designee

7.2.5.14.5 Hepatitis B, Hepatitis C, and HIV Status

Hepatitis B surface antigen, HBcAb, HepCAb, and HIV status will be assessed. If the results show a positive HepCAb: hepatitis C virus RNA by PCR is necessary. The test must be confirmed negative at screening for the subject to be eligible for this study.

7.2.5.14.6 Pregnancy Test (Females Only)

A serum pregnancy test will be performed on all female subjects at screening. A serum or urine pregnancy test will be collected on all female subjects at day -1 and EOS as specified in the Schedule of Assessments (Table 4 and Table 5). The screening (serum) and day -1 (serum or urine) pregnancy test must be confirmed negative for the subject to be eligible for this study.

Female subjects who become pregnant during the study will be followed for safety until end of study. A Pregnancy Notification Worksheet (Appendix C) will be completed for subjects with a positive test result at any point after providing informed consent.

7.2.5.14.7 Serum Follicle Stimulating Hormone Test (Females Only)

Additional serum may be collected for an FSH test if required to ensure menopause in a female subject. Results must be consistent with postmenopausal status per local laboratory ranges for inclusion in this study. Postmenopausal status will be recorded on the medical history CRF.

7.2.5.14.8 Drug and Alcohol Screen

A urine screen for drugs with a high potential of abuse (according to the local lab standards) will be performed at time points specified in the Schedule of Assessments (Table 4 and Table 5).

Table 9. Drug Screen Panel

Tetrahydrocannabinol	Benzodiazepines
Cocaine	Opiates
Amphetamines	Barbiturates
Ethanol (may be performed by a breath test)	

Subjects with a positive result at time points specified in the Schedule of Assessments will be excluded from the study. The intention is to detect drugs of abuse and not those prescribed therapeutically. Subjects with a positive drug test may be retested once at the discretion of the Principal Investigator in consultation with the Amgen Medical Monitor. The result will be documented in the source document but will not be recorded on the CRF.

7.2.5.14.9 Lipid Panel

A fasting (at least 10 hours) blood sample for total cholesterol, LDL-C (calculated), HDL-C, and triglycerides will be assessed at screening (ie, the screening lipid panel) and analyzed at the local laboratory. Fasting (at least 10 hours) blood samples for total cholesterol, LDL-C (by ultracentrifugation), HDL-C, triglycerides, apoA1, and ApoB will be assessed at all time points indicated as the on-study lipid panel in the Schedule of Assessments (Table 4 and Table 5) and analyzed at the central laboratory.

7.2.5.14.10 Alkaline Phosphatase Isoenzymes

Alkaline phosphatase isoenzymes including but not limited to bone specific alkaline phosphatase and liver specific alkaline phosphatase will be assessed at time points indicated in the Schedule of Assessments (Table 4 and Table 5).

7.2.5.15 AMG 529 Serum Concentrations for Pharmacokinetic Analysis

Blood samples for determination of AMG 529 serum concentrations will be assessed at time points indicated in the Schedule of Assessments (Table 4 and Table 5).

The PK samples are to be collected within the following windows:

- ± 10 minutes on day 1
- ± 1 hour on days 2-6
- ± 1 day on days 8-22
- + 3 days on day 30
- ± 3 days on days 43 and 57

The precise time of the sample collection should be documented.

Sample collection, processing, storage and shipping instructions are provided in the laboratory manual.

7.3 Antibody Testing Procedures

Blood samples will be collected at baseline and at the EOS visit as outlined in the Schedule of Assessments for the measurement of anti-AMG 529 antibodies. The analysis of anti-AMG 529 antibodies will be conducted on these samples only if there are unexpected PK findings or a safety signal in the study or future studies that warrants further investigation by characterizing drug immunogenicity. Samples testing positive may be further characterized for quantity/titer, isotype, affinity, and/or in vitro neutralizing activity. If the anti-AMG 529 antibody samples are analyzed, subjects who test positive for binding antibodies at the final scheduled study visit and have clinical sequelae that are considered potentially related to an anti-AMG 529 antibody response may also be asked to return for additional follow-up testing. This testing should occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks). All follow up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month), or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive AMG 529.

Refer to the Schedule of Assessments (Table 4 and Table 5) as applicable, for specific time points and the laboratory manual for detailed collection and handling instructions.

7.4 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 529, follow the pharmacologic response to AMG 529, and to further understand cardiovascular disease.

Blood samples are to be collected for biomarker development.

Refer to the Schedule of Assessments for specific time points and the laboratory manual for detailed collection and handling instructions.

7.5 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of coronary artery disease and/or to identify subjects who may have positive or negative response to AMG 529. Additional samples are collected for this part of the study.

Refer to the Schedule of Assessments for specific time points and the laboratory manual for detailed collection and handling instructions.

For subjects who consent to this/these analysis/analyses, DNA may be extracted.

7.6 Approximate Phlebotomy Volume

Subjects enrolled in this study will agree to provide whole blood for safety, PK, PD, biomarker and other assessments during their participation in this study as noted in Table 10, Table 11 and Table 12 below:

Table 10. Approximate Blood Volume Collection for Cohorts 1 (21 mg SC) and 2 (70 mg SC)

Test	Volume per Collection, mL	Number of Collections	Total Volume, mL
Clinical chemistry	8.5	11	93.5
Clinical hematology	4	6	24
Coagulation labs	2.7	7	18.9
Screening lipid panel*	8.5	1	N/A
On-study lipid panel	9	6	54
Pregnancy test (females only)*	8.5	1	N/A
HIV, HBSAg, HBcAb, HepCAb	8.5	1	8.5
Serum FSH (females only)*	8.5	1	N/A
Blood for biomarker development	14.5	4	58
Alkaline phosphatase isoenzyme	5	4	20
Pharmacogenetics (optional)**	3	1	N/A
AMG 529 PK serum concentration	5	13	65
Anti-AMG 529 Antibody	5	2	10
TOTAL			351.9

* Collected in the same tube as Clinical chemistry lab
** Obtained from cell pellet from the biomarker plasma sample collection at pre-dose (day 1) only

Table 11. Approximate Blood Volume Collection for Cohorts 3 (210 mg SC), 4 (420 mg SC), and 5 (700 mg SC)

Test	Volume per Collection, mL	Number of Collections	Total Volume, mL
Clinical chemistry	8.5	13	110.5
Clinical hematology	4	7	28
Coagulation labs	2.7	8	21.6
Screening lipid panel*	8.5	1	N/A
On-study lipid panel	9	7	63
Pregnancy test (females only)*	8.5	1	N/A
HIV, HBSAg, HBcAb, HepCAb	8.5	1	8.5
Serum FSH (females only)*	8.5	1	N/A
Blood for biomarker development	14.5	4	58
Alkaline phosphatase isoenzyme	5	4	20
Pharmacogenetics (optional)**	3	1	N/A
AMG 529 PK serum concentration	5	15	75
Anti-AMG 529 Antibody	5	2	10
TOTAL			394.6

* Collected in the same tube as Clinical chemistry lab
** Obtained from cell pellet from the biomarker plasma sample collection at pre-dose (day 1) only

Table 12. Approximate Blood Volume Collection for Cohort 6 (70 mg IV)

Test	Volume per Collection, mL	Number of Collections	Total Volume, mL
Clinical chemistry	8.5	11	93.5
Clinical hematology	4	6	24
Coagulation labs	2.7	7	18.9
Screening lipid panel*	8.5	1	N/A
On-study lipid panel	9	6	54
Pregnancy test (females only)*	8.5	1	N/A
HIV, HBSAg, HBcAb, HepCAb	8.5	1	8.5
Serum FSH (females only)*	8.5	1	N/A
Blood for biomarker development	14.5	4	58
Alkaline phosphatase isoenzyme	5	4	20
Pharmacogenetics (optional)**	3	1	N/A
AMG 529 PK serum concentration	5	15	75
Anti-AMG 529 Antibody	5	2	10
TOTAL			361.9

* Collected in the same tube as Clinical chemistry lab
** Obtained from cell pellet from the biomarker plasma sample collection at pre-dose (day 1) only

7.7 Sample Storage and Destruction

Any blood, biomarker, and PK samples collected according to the Schedule of Assessments (Table 4 and Table 5) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand cardiovascular diseases, the dose response and/or prediction of response to AMG 529, characterize antibody response, and characterize aspects of the molecule

(eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the Investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 4 and Table 5) including different

options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, and adverse events. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, medical device(s), and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, protocol deviation, non-compliance, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI) (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product (AMG 529 or placebo) through the End of Study are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to IP (AMG 529 or placebo)
- Assessment of relatedness to any study-mandated activity/procedure
- Action taken.

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.

The investigator must assess whether the adverse event is possibly related to the administration of investigational product (AMG 529 or placebo). This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product (AMG 529 or placebo)? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator must assess whether the adverse event is possibly related to any study mandated activity (eg, administration of investigational product and/or study procedure, including screening procedures). This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product and/or study procedure)?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of study visit are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Serious Adverse Event Report Form. Information submitted about the serious adverse event must be consistent with that recorded on the Event CRF. See Appendix B for a sample of the Serious Adverse Event Report (SAER) Form.

The investigator must assess whether the serious adverse event is possibly related to the administration of investigational product (AMG 529 or placebo). This relationship is

indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product (AMG 529 or placebo). Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator must assess whether the serious adverse event is possibly related to any study mandated activity (eg, administration of investigational product and/or study procedure, including any screening procedures). This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product and/or study procedure)?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local regulatory requirements and procedures.

9.2.1.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after the end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

See Appendix B for a sample of the Serious Adverse Event Report (SAER) Form.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking protocol-required therapies, AMG 529 or placebo, report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 90 days after the last dose of AMG 529.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female subject breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 90 days after the last dose of protocol-required therapies.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix D). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

- Subject incidence of treatment-emergent adverse events
- Safety laboratory analytes, vital signs, and ECGs

10.1.1.2 Secondary Endpoints

- 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)

10.1.1.3 Exploratory Endpoints

- 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

10.1.2 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.

10.1.2.1 Safety Analysis Set

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

10.1.2.2 Pharmacokinetic Analysis Set

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

10.1.2.3 Pharmacodynamics Analysis 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.

10.1.3 Covariates and Subgroups

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.

No subgroup analyses are planned. Within each cohort, subjects will be randomized so that 6 subjects receive AMG 529 and 2 subjects receive placebo in each cohort. Data from placebo-treated healthy subjects will be pooled across the cohorts for analysis.

10.2 Sample Size Considerations

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%.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Amgen staff and their designees involved in the study will not be blinded, but will only be given treatment assignments when there is a need to use the information for analysis, discussion and internal decision making. The Amgen Medical Monitor will be unblinded to treatment assignment throughout the duration of the study. Access to treatment assignments and other restricted data are described in Amgen standard documents. Unblinded individuals are to ensure unblinding and potentially

unblinding information should not be distributed to the investigators or subjects prior to the study being formally unblinded.

10.4 Planned Analyses

10.4.1 Dose Level Review Meeting (DLRM)

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, the unblinded 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). Except for the unblinded Amgen Medical Monitor who will review data in an unblinded manner, DLRMs will be conducted in a blinded manner.

10.4.2 Primary Analysis

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

10.4.3 Final Analysis

The primary analysis will be the final analysis.

10.5 Planned Methods of Analysis

10.5.1 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.

10.5.2 Primary Endpoints

10.5.2.1 Safety Endpoints

10.5.2.1.1 Adverse 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 (MedDRA) terminology. Tables of adverse events, fatal adverse events, and serious adverse events will also be provided if observed.

10.5.2.1.2 Vital Signs

Subject-level data for vital signs including blood pressure, heart rate, respiratory rate, and body temperature 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.

10.5.2.1.3 Electrocardiogram

All on-study ECG data will be listed and may be plotted. Summaries over time and/or changes from baseline over time will be provided for all ECG parameters (eg, RR, PR, QRS, QTc). Subjects' maximum change from baseline in QTcF will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post-baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. Baseline ECG recording is defined as the mean of the 3 sets of triplicate ECG results at stud day 1 pre-dose (a total of 9 assessments).

10.5.2.1.4 Clinical Laboratory

Analyses of laboratory values 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.

10.5.3 Secondary Endpoints

10.5.3.1 Pharmacokinetics 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.

10.5.3.2 Alkaline Phosphatase

Analyses of ALP values 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.

10.5.3.3 Lipid Levels

Analyses of total cholesterol, LDL-C, 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.

10.5.4 Exploratory Endpoints

The statistical analyses in this section are considered exploratory in nature and will be performed only when deemed appropriate.

10.5.4.1 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.

10.5.4.2 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.

10.5.4.3 Potential Biomarkers

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

10.5.4.4 Antibody Analysis

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.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated

formally in writing from the Amgen Study Manager to the investigator. The written ICF is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any investigational product(s) is/ are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or

serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in strict confidence by the investigator, except as described below.

In compliance with governmental/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named such individuals to have access to his/her study related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, the Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s), and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRF, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 4 and Table 5), the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, the investigator will obtain input and assistance from Amgen staff as appropriate.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

13. REFERENCES

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

Bovenschen N, Rijken DC, Havekes LM et al. The B domain of coagulation factor VIII interacts with the asialoglycoprotein receptor. *Thromb Haemost*. 2005;3:1257–1265.

Burger RL, Schneider RJ, Mehlman CS, Allen RH. Human plasma R-type vitamin B12-binding proteins II. The role of transcobalamin I, transcobalamin III, and the normal granulocyte vitamin B12-binding protein in the plasma transport of vitamin B12. *J Biol Chem*. 1975;250(19):7707-7713.

EMEA. Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products. EMEA/CHMP/SWT/28367/07. 19 July 2007.

Ellies LG, Ditto D, Levy GG, et al. Sialyltransferase ST3Gal-IV operates as a dominant modifier of hemostasis by concealing asialoglycoprotein receptor ligands. *PNAS*. 2002;99(15):10042-10047.

Food and Drug Administration. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. July 2005.

Hardonk MJ, Scholtens HB. A histochemical study about the zonal distribution of the galactose-binding protein in rat liver. *Histochemistry and Cell Biology*. 1980;69(3):289-297.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2013. http://www.icmje.org/

Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet*. 1999;353:89-92.

Mensah GA, Wei GS, Sorlie PD, et al. Decline in cardiovascular mortality: possible causes and implications. *Circ Res*. 2017;120:366-380.

Mortensen B, Huseby NE. Clearance of circulating gamma-glutamyltransferase by asialoglycoprotein receptor. Enzyme forms with different sialic acid content are eliminated at different clearance rates and without apparent desialylation. *Clinica Chimica Acta*. 1997;258:47-58.

Mozaffarian D, Benjamin EJ, Go AS et al. Executive summary: heart disease and stroke statistics - 2016 update: a report from the American Heart Association. *Circulation*. 2016a;133:447-454.

Mozaffarian D, Benjamin,EJ, Go, AS, et al. Heart disease and stroke statistics - 2016 update: a report from the American Heart Association. *Circulation*. 2016b;133:e38-e360.

Nioi P, Sigurdsson A, Thorleifsson G, et al. Variant ASGR1 associated with a reduced risk of coronary artery disease. *N Engl J Med*. 2016;374(22):2131-2141.

Pricer WE, Ashwell G. The binding of desialylated glycoproteins by plasma membranes of rat liver. *J Biol Chem*. 1971;246(15):4825-4833.

Seested T, Nielsen HM, Christensen EI, Appa RS. The unsialylated subpopulation of recombinant activated factor VII binds to the asialo-glycoprotein receptor (ASGPR) on primary rat hepatocytes. *Thromb Haemost*. 2010;104(6):1166-1173.

United States Food and Drug Administration. Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation, 2009.

Weigel PH, Yik JHN. Glycans as endocytosis signals: the cases of the asialoglycoprotein and hyaluronan/chondroitin sulfate receptors. *Biochim Biophys Acta*. 2002;1572(2):341-363.

World Health Organization. Cardiovascular diseases (CVDs): fact sheet. September 2016. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed February 2017.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.3 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.1.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.3.1 or who experience AST or ALT elevations > 3 x ULN or 2-fold increase above baseline values for subjects with evaluated values before drug are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Serum acetaminophen (paracetamol) levels
  - A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents

  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- CPK, haptoglobin, LDH, and peripheral blood smear
- Appropriate liver imaging if clinically indicated

- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

Appendix B. Sample Serious Adverse Event Report Form

A **AMG 529** **20160138**	**Clinical Trial Serious Adverse Event Report** **Phase 1–4** ***Notify Amgen Within 24 Hours of knowledge of the event***	☐**New** ☐**Follow-up**

SELECT OR TYPE IN A FAX#
US: +888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth Day Month Year	Sex	Race
		☐F ☐M	

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day_____Month____Year_____

Serious Adverse Event Diagnosis or Syndrome **If diagnosis is unknown, enter Signs / Symptoms** **When Final Diagnosis is known, enter as Adverse Event** *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the event may have been caused by **AMG 529?** **If yes see section 10** **No✓** **Yes✓**	**Relationship** Is there a reasonable possibility that the event may have been caused by an Amgen device? **No✓** **Yes✓** **If Yes, what device?**	**Outcome of Event** **01** Resolved **02** Resolving **03** Not resolved **04** Fatal	Check only if event is related to study procedure *eg, biopsy*

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted Day Month Year	**Date Discharged** Day Month Year
Was subject hospitalized? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	**Prior to, or at time of Event** **Date of Dose** Day Month Year	**Dose**	**Route**	**Frequency**	**Action Taken with Product** **01** Still being Administered **02** Permanently discontinued **03** Withheld

AMG 529 *(Blinded)*						

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

Site Number	Subject ID Number

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date Day Month Year	Test / Unit										

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** For each event in section 3, where relationship=Yes, please provide rationale.		
Signature of Investigator or Designee	Title	Date

Appendix C. Pregnancy Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: AMG 529 20160338

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm___/ dd___/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm___/dd___/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm___/dd___/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm___/ dd___/ yyyy____ ☐ Unknown

Estimated date of delivery mm___/ dd___/ yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___/ dd___/ yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm___/dd___/yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

Appendix D. Lactation Notification Worksheet

AMGEN® Lactation Notification Worksheet

*Fax Completed Form to the Country-respective Safety Fax Line **

SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: AMG 529 20160338

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ /dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Amendment 1

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

Amgen Protocol Number AMG 529 20160338

Amendment Date: 01 May 2017

Rationale:

The following updates were made to the protocol, dated 23 February 2017:

- Incorporate changes as requested by the FDA including:
  - The Amgen medical monitor is unblinded and will monitor data on an ongoing basis throughout the duration of the study. The unblinded medical monitor may suspend dosing and convene a DLRM based on emerging safety data.
  - The Amgen medical monitor will seek as necessary consultation from a hematologist for changes in coagulation tests (see Section 7).
  - Stopping rules will be revised based on “mild, moderate, severe” grading and not CTCAE grading. In addition, the team has removed all CTCAE grading from the protocol and will grade all AEs based on the grading system as follows: grade 1 = mild; grade 2 = moderate; grade 3 = severe; grade 4 = life-threatening; and grade 5 = fatal (each grade is described further in the protocol amendment).
- Mean platelet volume was added as a hematology parameter.
- In addition, typographical errors and inconsistencies between sections throughout the protocol were corrected.

Description of Changes:

Section 6.2.1.2.1, 1st paragraph

Added bolded item:

Dose Level Review Meetings will be held to review data, monitor safety and make dose change decisions. The Dose Level Review Meeting (DLRM) members will be composed of the principal investigator or designee, the **unblinded** Amgen Medical Monitor, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager or designee, and biostatistics representative or designee. Additional members may be added as needed (eg, clinical pharmacology scientist). The DLRM voting members include the principal investigator or designee, Amgen Medical Monitor and Amgen Global Safety Officer or designee.

Section 6.2.1.2.1, 3rd paragraph

Added bolded items:

Except for the unblinded Amgen Medical Monitor who will review data on an ongoing basis throughout the duration of study in an unblinded manner, data will be reviewed by the rest of the DLRM members in a blinded manner (ie, treatment assignment will not be revealed) unless unblinding is deemed necessary for the review team to make dosing decisions. **Unblinding can be performed at any time by the investigator or Amgen if deemed necessary for subject safety.** If deemed necessary, unblinding will be performed according to Amgen standard procedures.

Section 6.2.1.2.2, 1st paragraph

Deleted strikethrough text and added bolded items:

- Determination of the severity of adverse events will be ~~consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix A).~~**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.**

Section 6.2.1.2.2, 2nd paragraph

Added bolded items:

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.**

Section 6.2.1.2.2, 4th paragraph

Deleted strikethrough text:

~~The study may be terminated at any point in time at the discretion of the sponsor or the investigator.~~

Section 6.2.1.2.2, Table 3

Deleted strikethrough text and added bolded items:

Table 3. Cohort Dose Stopping Rules

Scenario	Action

Any occurrence of a ~~CTCAE v.4~~ 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 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

Page 1 of 2

Footnotes defined on next page of the table

Table 3. Cohort Dose Stopping Rules

Scenario	Action
Any occurrence of a ~~CTCAE v.4~~ 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: o resume enrollment of the cohort as planned o resume enrollment of the cohort at a lower dose o expand the cohort at the same dose o add a lower dose cohort to the study o escalate to an intermediate dose (a dose lower than the next planned dose) o escalate to the next planned dose

Page 2 of 2

[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

Section 7.1, Table 4. Schedule of Assessments for Cohorts 1, 2, and 6

Added bolded item:

Activity	Screening		Treatment															EOS
Study Day	(-28 to -2)	-1	1						2	3	4	6	8	11	15	22	30	
Time (in hours) [a]			Pre-Dose	0	0.5	1	6	12	24	36	48	72	120	168	240	336	504	696
Informed Consent	X																	
In-House Residency		X	<-															-> X
Medical History	X	X																
Body Weight	X																	X
Body Mass Index	X																	
Height	X																	
Vital Signs (HR, RR, BP, TEMP)	X	X	X			X [c]	X	X	X		X	X	X	X	X	X	X	X
Physical Examination	X	X																X
12-lead ECG [b]	X		X			X [c]	X	X	X		X	X	X	X	X	X	X	X
eGFR	X	X																X
Clinical Chemistry [d]	X	X							X		X [e]	X	X [e]	X [e]	X	X [e]	X	X
Clinical Hematology	X	X							X			X			X		X	X
PT/INR and aPTT	X	X							X			X			X		X	X
Urinalysis	X	X							X			X			X		X	X
Screening Lipid Panel [d]	X																	
On-study Lipid Panel [d]			X								X		X		X		X	X
Drug and Alcohol Screen	X	X																
HIV, HBsAg, HBcAb, HepCAb [f]	X																	
Pregnancy Test (females only)	X	X																X
Serum FSH Test (females only) [g]	X																	
Randomization		X																
Study Drug Administration				X														
Anti-Drug Antibody Sample Collection			X															X
PK Sample Collection (SC cohorts only)			X [h]				X	X	X	X	X	X	X	X	X	X	X	X
PK Sample Collection (IV cohort only)			X [h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alkaline phosphatase isoenzymes			X								X		X					X
Collect blood for biomarker development [i]			X								X		X					X
Pharmacogenetic (optional) [i]			X															
Adverse Event Recording				X	<-													-> X
Serious Adverse Event Recording	X	<-																-> X
Concomitant Medications	X	<-																-> X

Section 7.1, Table 5. Schedule of Assessments for Cohorts 3, 4, and 5

Deleted strikethrough text, added bolded items:

Activity	Screening		Treatment														EOS
Study Day	(-28 to -2)	-1	1			2		3	4	6	8	11	15	22	30	43	57
Time (in hours) [a]			Pre-Dose	0	6	12	24	36	48	72	120	168	240	336	504	696	1008	1344
Informed Consent	X																	
In-House Residency		X	<-															-> X
Medical History	X	X																
Body Weight	X																	X
Body Mass Index	X																	
Height	X																	
Vital Signs (HR, RR, BP, TEMP)	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X													X			X
12-lead ECG [b]	X		X		X	X	X		X	X	X	X	X	X	X	X	X	X
eGFR	X	X																X
Clinical Chemistry [c]	X	X					X		X [d]	X	X [d]	X [d]	X	X [d]	X	X	X [d]	X
Clinical Hematology	X	X					X		X		X		X	X				X
PT/INR and aPTT	X	X					X		X		X		X	X				X
Urinalysis	X	X					X		X		X		X	X				X
Screening Lipid Panel [c]	X																	
On-study Lipid Panel [c]			X						X		X		X		X	X		X
Drug and Alcohol Screen	X	X																
HIV, HBsAg, HBcAb, HepCAb [e]	X																	
Pregnancy Test (females only)	X	X																X
Serum FSH Test (females only) [f]	X																	
Randomization		X																
Study Drug Administration				X														
Anti-Drug Antibody Sample Collection			X															X
PK Sample Collection			X [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alkaline phosphatase isoenzymes			X						X		X				X			
Collect blood for biomarker development [h]			X						X		X				X			
Pharmacogenetic (optional) [i]			X															
Adverse Event Recording				X	<-													-> X
Serious Adverse Event Recording	X	<-																-> X
Concomitant Medications	X	<-																-> X

[a] Time in hours are relative to IP administration
[b] A single ECG will be collected at screening. Prior to dosing day 1, 3 baseline ECGs will be collected approximately 30 minutes apart. Each baseline ECG will be in triplicate to be collected 30 seconds apart for a total of 9 ECGs. Triplicate ECGs, to be collected 30 seconds apart, will be collected at all timepoints after dosing on day 1.
[c] 10 hour fasting is required at all time points
[d] Alkaline phosphatase only on days 3, 6, 8, ~~and~~ 15 **and 43**
[e] If the results show a positive HepCAb: hepatitis C virus RNA by PCR is necessary. The test must be confirmed negative at screening for the subject to be eligible for this study.
[f] Serum FSH Test (females only) for postmenopausal status will be conducted as per Section 7
[g] Pre-dose PK sample will be collected approximately 1 hour prior to dosing
[h] Biomarker samples (plasma and serum) to be collected on days 1, 3, 8, and 30
[i] Pharmacogentic sample obtained from cell pellet from the biomarker plasma sample collection at pre-dose (day 1) only

Section 7.2.5.5, Medical History

Deleted strikethrough items, added bolded items:

A complete medical history will be obtained at screening by the investigator or designated site physician. Medical history will include information on the subject's current health and surgical history. Relevant medical history findings will be recorded in the subject's source and on the appropriate pages of the CRF. Any unresolved medical history will be graded **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.** ~~according to Common Toxicology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix A) unless specified otherwise~~.

Section 7.2.5.14.1, Hematology

Added bolded items:

Table 6. Hematology Panel

Red Blood Cells	White Blood Cells
Hemoglobin	• Total neutrophils
Hematocrit	• Eosinophils
Mean Corpuscular Volume	• Basophils
Platelet count	• Lymphocytes
Mean Platelet Volume	• Monocytes

Section 7.2.5.14.2, Coagulation Tests

Added bolded items:

The following coagulation tests will be performed: prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). **The unblinded Amgen Medical Monitor will obtain, as necessary, consultation with a hematologist for changes in coagulation tests.**

Section 7.6, Tables 10, 11 and 12

Deleted strikethrough items, added bolded items:

Table 10. Approximate Blood Volume Collection for Cohorts 1 (21 mg SC) and 2 (70 mg SC)

Test	Volume per Collection, mL	Number of Collections	Total Volume, mL
Clinical chemistry	8.5	11	93.5
Clinical hematology	4	6	24
Coagulation labs	~~3~~**2.7**	7	~~21~~ **18.9**
Screening lipid panel*	8.5	1	N/A
On-study lipid panel	9	6	54
Pregnancy test (females only)*	8.5	1	N/A
HIV, HBSAg, HBcAb, HepCAb	8.5	1	8.5
Serum FSH (females only)*	8.5	1	N/A
Blood for biomarker development	14.5	4	58
Alkaline phosphatase isoenzyme	5	4	20
Pharmacogenetics (optional)**	3	1	N/A
AMG 529 PK serum concentration	5	13	65
Anti-AMG 529 Antibody	5	2	10
TOTAL			351.**9**

* Collected in the same tube as Clinical chemistry lab
** Obtained from cell pellet from the biomarker plasma sample collection at pre-dose (day 1) only

Table 11. Approximate Blood Volume Collection for Cohorts 3 (210 mg SC), 4 (420 mg SC), and 5 (700 mg SC)

Test	Volume per Collection, mL	Number of Collections	Total Volume, mL
Clinical chemistry	8.5	13	110.5
Clinical hematology	4	7	28
Coagulation labs	**2.7 ~~3~~**	8	**21.6 ~~24~~**
Screening lipid panel*	8.5	1	N/A
On-study lipid panel	**9 ~~8.5~~**	7	**63 ~~59.5~~**
Pregnancy test (females only)*	8.5	1	N/A
HIV, HBSAg, HBcAb, HepCAb	8.5	1	8.5
Serum FSH (females only)*	8.5	1	N/A
Blood for biomarker development	14.5	4	58
Alkaline phosphatase isoenzyme	5	4	20
Pharmacogenetics (optional)**	3	1	N/A
AMG 529 PK serum concentration	5	15	75
Anti-AMG 529 Antibody	5	2	10
TOTAL			**394.6**

* Collected in the same tube as Clinical chemistry lab
** Obtained from cell pellet from the biomarker plasma sample collection at pre-dose (day 1) only

Table 12. Approximate Blood Volume Collection for Cohort 6 (70 mg IV)

Test	Volume per Collection, mL	Number of Collections	Total Volume, mL
Clinical chemistry	8.5	11	93.5
Clinical hematology	4	6	24
Coagulation labs	**2.7** ~~3~~	7	**18.9**
Screening lipid panel*	8.5	1	N/A
On-study lipid panel	**9** ~~8.5~~	6	**54**
Pregnancy test (females only)*	8.5	1	N/A
HIV, HBSAg, HBcAb, HepCAb	8.5	1	8.5
Serum FSH (females only)*	8.5	1	N/A
Blood for biomarker development	14.5	4	58
Alkaline phosphatase isoenzyme	5	4	20
Pharmacogenetics (optional)**	3	1	N/A
AMG 529 PK serum concentration	5	15	75
Anti-AMG 529 Antibody	5	2	10
TOTAL			**361.9**

* Collected in the same tube as Clinical chemistry lab
** Obtained from cell pellet from the biomarker plasma sample collection at pre-dose (day 1) only

Section 9.2.1.1, 3rd paragraph

Deleted strikethrough text and added bolded items:

Determination of the severity of adverse events will be ~~consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix A).~~**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.**

Section 9.3, 2nd paragraph

Deleted strikethrough text and added bolded items:

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 4 ~~**weeks**~~**90 days** after the last dose of AMG 529.

Section 9.3, 7th paragraph

Deleted strikethrough items, added bolded items:

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through ~~4 weeks~~ **90 days** after the last dose of protocol-required therapies.

Section 10.3, 1st paragraph

Added bolded items:

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Amgen staff and their designees involved in the study will not be blinded, but will only be given treatment assignments when there is a need to use the information for analysis, discussion and internal decision making. **The Amgen Medical Monitor will be unblinded to treatment assignment throughout the duration of the study.**

Section 10.4.1, 1st paragraph

Added bolded items:

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, **the unblinded** 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). **Except for the unblinded Amgen Medical Monitor who will review data in an unblinded manner**, DLRMs will be conducted in a blinded manner.

Appendix A, 1st paragraph

Deleted strikethrough items:

~~The CTCAE Version 4.0 is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronicapplications/ctc.htm.~~