STATISTICAL ANALYSIS PLAN

A Randomized, Double Blind Placebo Controlled, First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Sub-cutaneous Doses of AMG 570 in Healthy Subjects

Protocol Number 20140322

Version: **3.0**

Date: **26 March 2018**

Authors: [redacted]

NCT Number: NCT02618967
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

Table of Contents

List of Tables

List of Appendices

Table of Abbreviations

Abbreviation or Term	Definition/Explanation
ADA	Anti-drug antibodies
AUC	Area under concentration time curve
[redacted]	[redacted]
B7RP-1	B7-related protein-1
BMI	body mass index
C_{max}	maximum observed concentration
CL	total systemic clearance
CRF	case report form
Css	Steady state plasma concentration
DILI	drug-induced livery injury
DLRM	dose level review meeting
DLT	dose limiting toxicity
ECG	Electrocardiogram
eCRF	electronic case report form
end of study for individual subject	defined as the last date that protocol-specified procedures are conducted for an individual subject
end of treatment	defined as the date of final assessment for the protocol specified treatment phase of the study for an individual subject
end of study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s).
end of trial	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up), the end of study would include these additional parts
FIH	First in Human
Ig	Immunoglobulin
ICF	informed consent form
IP	Investigational Product
IPRO	Immunophenotyping and Receptor Occupancy
LLOQ	lower limit of quantification
PD	pharmacodynamic
PK	pharmacokinetic
PR	the interval measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by electrocardiogram

Abbreviation or Term	Definition/Explanation
QRS	the interval between the Q wave and the S wave in the heart's electrical cycle as measured by electrocardiogram; represents the time it takes for depolarization of the ventricles
QT	measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by electrocardiogram
RO	receptor occupancy
RR	Respiratory Rate
SC	Subcutaneous
SLE	Systemic Lupus Erythematosus
study day 1	defined as the first day that protocol specified investigational product is administered to the subject
t_{max}	time to maximum concentration
Vss	the volume of distribution at steady state

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amdendment for AMG570 Study 20140322 dated 24 January 2018. The scope of this plan includes the primary analysis that are planned at the primary completion of the study and will be executed by the Global Biostatistical Sciences (GBS) unless otherwise specified.

2. Objectives

2.1 Primary

- To assess the safety and tolerability of single subcutaneous (SC) doses of AMG 570 in healthy subjects

2.2 Secondary

- To characterize the PK profile of single subcutaneous (SC) doses of AMG 570 in healthy subjects
- To evaluate the PD effects (B7RP-1 occupancy and inhibition of B cell survival) of single subcutaneous (SC) doses of AMG 570 in healthy subjects
- To evaluate the immunogenicity of AMG 570

2.3 Exploratory

- To evaluate the relationship between PK, B7RP-1 occupancy, [redacted] and changes in percentage and absolute counts of naïve and memory B cells following single subcutaneous (SC) doses of AMG 570 in healthy subjects
- To evaluate the PD effect of single subcutaneous (SC) doses of AMG 570 in healthy subjects on serum IgG and IgM

3. Study Overview

3.1 Study Design

This is a randomized, placebo-controlled, double-blind, single ascending dose (SAD) study in healthy subjects. The study consists of 6 SC cohorts. Subjects will be randomized in a 3:1 ratio to receive AMG 570 or placebo according to Table 1.

Table 1. Dose Levels

Cohort #	Planned Dose (mg)	Route	N(active:placebo)
1	7	SC	8 (6:2)
2	21	SC	8 (6:2)
3	70	SC	8 (6:2)
4	140	SC	8 (6:2)
5	210	SC	8 (6:2)
6	420	SC	8 (6:2)
7	700	SC	8 (6:2)

Subject will be randomized only once to one of 7 Cohorts starting with Cohort 1 and continuing in a sequential manner to Cohort 7. Within each cohort, subjects will be randomized to receive a single SC dose of AMG 570 or placebo in a ratio of 3:1. Once a dose is selected for a cohort, no dose adjustments will be made for an individual subject within the cohort. Each subject will only receive one dose of the investigation product.

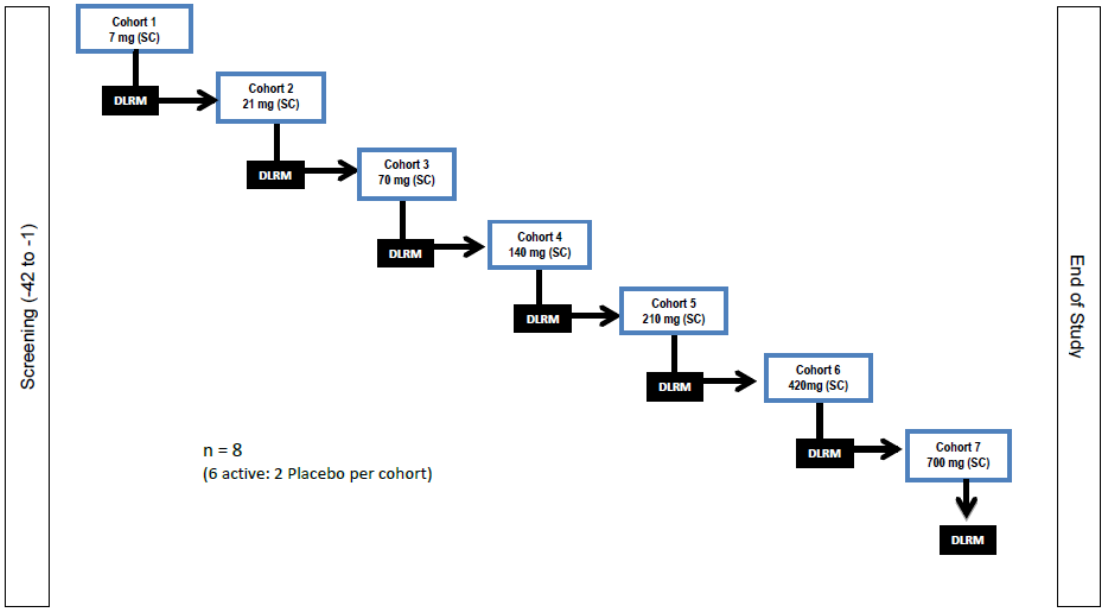
A sentinel dosing strategy will be used. The first 2 subjects in each cohort will be randomized such that 1 subject receives AMG 570 and 1 subject receives placebo. This sentinel pair will be dosed first and will be observed for at least 24 hours before study drug is administered to the remainder of the cohort. An informal safety review will be held after the sentinel subjects of each cohort are dosed and prior to dosing the subsequent 6 subjects. The decision to continue with the cohort as planned will be based on available data for vital signs and adverse events occurring in the prior 24 hours, and will be reviewed by the PI, medical monitor or designee, and GSO or designee.

The decision to dose escalate for the next cohort will be based on the review of safety data from the previous cohort during the dose level review meeting. Within each cohort, the safety data will be assessed after all 8 subjects have been enrolled and at least 6 subjects have completed the day 57 visit.

Emerging PK and PD data will be reviewed in a blinded fashion at the DLRM as these data become available. Peripheral blood B cell number and serum IgG levels through day 57 post-dose for individual cohorts will be incorporated into each DLRM assessment.

For the schedule of assessment, please refer to Appendix A. For further details on the study design refer to Section 3 of the protocol.

3.1.1 Study Design and Treatment Schema



3.2 Sample Size

Approximately 56 healthy subjects will be enrolled into 7 cohorts (6 active: 2 placebo in each cohort). This sample size is based on practical considerations and is typical for this type of study. For safety considerations, for a cohort, with 6 subjects receiving AMG 570, there is an 82% chance of at least one subject experiencing an adverse event with a true incidence rate of 25% and a 74% chance of at least one subject experiencing an adverse event with 20% true incidence rate. With a total of 42 subjects expected to receive AMG 570 across all 7 cohorts, there is a 34% chance of at least 1 subject experiencing an adverse event with a true incidence rate of 1% and the chance of at least 1 subject experiencing an adverse event increases to 88% and 99% with a true incidence rate of 5% and 10%, respectively.

4. Study Endpoints And Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoints

- Subject incidences of treatment-emergent adverse events including clinically significant changes in physical examinations, vital signs, laboratory safety tests, and electrocardiograms (ECGs).

4.1.2 Secondary Endpoints

- AMG 570 PK parameters (eg, maximum observed concentration [C_{max}], time at C_{max} [t_{max},], and area under the concentration-time curve [AUC]).
- Anti-AMG 570 binding antibodies.

- Peripheral blood B7RP-1 receptor occupancy.
- Peripheral blood changes in percentage and absolute counts of naïve and memory CD19^{+} B cells (naïve = IgD^{+}CD27^{-}, memory = IgD^{-}CD27^{+}).

4.1.3 Exploratory Endpoints

Exploratory biomarkers may include but are not limited to the following:

- [redacted].
- Serum IgG and IgM.

4.2 Planned Covariates

No subgroup analysis is planned.

5. Hypotheses And/Or Estimations

A single SC dose administration of AMG 570 will achieve acceptable safety and tolerability profiles in healthy subjects within the proposed dose ranges (SC: 7 to 700 mg AMG 570).

6. Definitions

Age

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

$AUC_{0\text{-last}}$

Area under the concentration-time curve from time 0 (time of investigational product administration) to the time of the last quantifiable concentration.

$AUC_{0\text{-}\infty}$

Area under the concentration-time curve from time 0 (time of investigational product administration) to the infinity.

Baseline

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

ECG analysis value

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

that timepoint. Further, unscheduled ECG measurements taken up to 5 minutes after the last assessment of a triplicate at a timepoint will be included in the mean for that timepoint.

Baseline ECG

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

Bazett-corrected QT Interval (QTcB)

The Bazett correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows:

$QTcB=QT/(RR/1000)^{1/2}$

B7RP-1 Receptor occupancy (RO)

RO= [1 - (background subtracted free B7RP-1/ background subtracted total B7RP-1)/(Baseline background subtracted free B7RP-1 /Baseline background subtracted total B7RP-1)] * 100

Where,

background subtracted free B7RP-1= free B7RP-1 – Maximally saturated free B7RP-1

background subtracted total B7RP-1= total B7RP-1 – background subtraction factor

where the background subtraction factor is 171, 208 and 96 for Total B cells, Memory B cells and Monocytes respectively.

RO is 0 at baseline.

Change From Baseline

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

C_{max}

Maximum observed serum concentration.

End-of-Study

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

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

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

Enrollment Date

Enrollment date is defined as the randomization date.

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows:

$QTcF=QT/(RR/1000)^{1/3}$

Investigational Product

The term 'investigational product' is used in reference to AMG 570 or placebo.

Percent Change From Baseline

Percent change from Baseline is the arithmetic difference between post-Baseline and Baseline divided by Baseline values times 100.

Percent change from baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

Randomization Date

The date the subject was allocated to a randomization number.

Fold change from Baseline

Fold change from Baseline equals the post-Baseline value divide by the Baseline value.

Fold change from baseline = Post-baseline Value / Baseline Value

Study Day

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

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

Study Day 1

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

Treatment-Emergent Adverse Event (TEAE)

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

Treatment-Related AE

A treatment-related AE is any treatment-emergent adverse event that per investigator review has a reasonable possibility of being caused by the investigational product.

7. Analysis Subsets

For safety, pharmacokinetic concentration, pharmacokinetic parameter and pharmacodynamic analyses, subjects will be analyzed according to the treatment they received, not the treatment to which they were randomized.

7.1 Safety Analysis Set

The safety set will consist of all subjects who have received AMG 570/placebo.

7.2 Pharmacokinetic (PK) Concentration Analysis Set

The PK concentration analysis set will contain all subjects who have received AMG 570 and have at least one quantifiable PK sample collected.

7.3 Pharmacokinetic (PK) Parameter Analysis Set

The PK parameter analysis set will consist of all subjects who have received AMG 570 and for whom at least one PK parameter can be adequately estimated.

7.4 Pharmacodynamic (PD) Analysis Set

The PD analysis set will consist of all subjects who have received AMG 570/placebo and for whom at least one PD parameters have quantifiable baseline sample (not needed for B7RP1 occupancy) and at least one quantifiable post-baseline PD sample collected.

8. Interim Analysis And Early Stopping Guidelines

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

8.1 Dose Level Review Meeting (DLRM)

The DLRM members will be composed of the investigator(s), Amgen Medical Monitor, Amgen Global Safety Officer (GSO) or designee, Early Development Leader or designee, Clinical Study Manager or designee, and Biostatistics representative or designee. Additional members may be added as needed (eg, PK Scientist). The DLRM

voting members will include the investigator(s), Amgen Medical Monitor or designee, and Amgen GSO or designee.

8.1.1 Dose-cohort Study Escalation and Stopping Rules

Dose-Cohort Study Escalation

The DLRM voting members will be responsible for dosing decisions, which may include:

1) escalation to the next planned dose
2) escalation to an intermediate dose (a dose lower than the next planned dose)
3) de-escalation to a lower dose
4) continuation, delay, or termination of dosing
5) repetition or expansion of a cohort.

Dose adjustments (if any) will be made on a treatment cohort basis and not on an individual basis, and will be agreed upon by Amgen after reviewing emerging safety, PK, and/or PD data.

Dose Stopping and Review

Further dosing of AMG 570 will be either stopped or modified to a lower dose if suspected adverse drug reactions and/or changes in safety data (including but not limited to vital signs, ECGs, clinical laboratory results, or laboratory parameters reflecting humoral immune status) are observed and these changes pose a health risk. A DLRM is held when a dose limiting toxicity (DLT) has occurred. A DLT is defined as any treatment-related fatal, life threatening or disabling serious adverse event (SAE). In addition, any adverse event or change in vital signs, clinical laboratory test value, or ECG which is considered drug related, and poses a significant health risk, as determined by the Investigators and Sponsor, would also constitute a DLT and form the basis for stopping dose escalation in the study. If a decision is made not to proceed following dosing of sentinel subjects, a Dose Level Review Meeting (DLRM) will be held. In addition, dosing will be stopped or modified if any of the scenarios shown in Table 2 are met.

Dose Cohort Stopping Rules

This section addresses how subject safety will be monitored through adherence to rules for stopping dosing within a dose cohort (which precludes any further dose escalation). Table 2 describes the dose stopping rules to be used for stopping dosing within a cohort.

Table 2. Dose Cohort Stopping Rules

Scenario	Action
Any occurrence of a CTCAE **Grade 2** adverse event of the same system class (eg, hepatobiliary, cardiovascular) observed in 2 or more subjects in the same cohort	Stop dosing additional subjects in the cohort and convene DLRM. Review AE and all relevant safety data for evidence of relationship to treatment and clinical significance. Consider unblinding to determine relatedness to investigational product.* Upon unanimous decision of the review team, one of the following decisions may be made: • Enrollment of the cohort may resume, • The cohort may be expanded at the same dose, • A lower dose cohort may be added to the study, • Escalation to the next planned dose may occur, • Escalation to an intermediate dose (a dose lower than the next planned dose) may take place.
Any occurrence of a CTCAE **Grade 3 or greater** adverse event in a dose cohort	Stop dosing additional subjects in the cohort and convene DLRM. Review AE and all relevant safety data for evidence of relationship to treatment and clinical significance. Consider unblinding to determine relatedness to investigational product.* If Grade 3 adverse event is determined to be related to study drug, and clinically significant by the DLRM, no further dose escalation to proceed. Otherwise, upon unanimous decision of the review team, one of the following decisions may be made: • Enrollment of the cohort may resume, • The cohort may be expanded at the same dose, • A lower dose cohort may be added to the study.

* 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

For details on stopping rules for vital signs, ECG, laboratory data, humoral immune status, dose adjustments and hepatoxicity please refer to Section 6 of the protocol.

9. Data Screening And Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

Amgen's Clinical Data Management department will provide all data to be used in the planned analyses. The database will be subject to edit checks outlined in the Clinical Data Management Plan (DMP). See details of this section in the DMP.

9.3 Handling of Missing and Incomplete Data

The following imputation of missing values will be done:

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

9.4 Detection of Bias

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

9.5 Outliers

Details of detecting outliers can be found in the DMP or other data management document.

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

9.6 Distributional Characteristics

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

9.7 Validation of Statistical Analyses

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

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

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System and S-plus.

10. Statistical Methods Of Analysis

10.1 General Principles

Descriptive statistics will be provided for selected demographics, safety, immunogenicity, PK, PD, and biomarker data. 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 and by time as appropriate. Graphical summaries of the data may also be presented. When data are summarized by time, the scheduled time points listed in the protocol will be used. For statistical analyses comparing change from baseline, only subjects with both baseline and at least one post-baseline assessment will be included. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used.

Only critical subject-level data listings will be provided. Additional listings of subject-level data will be reviewed during DLRM meetings for assessment of subjects' safety and as part of ongoing data review to check the quality of data, but will not be included in the clinical study report to protect subjects' privacy.

10.2 Subject Accountability

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

Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

A subject listing will be provided for randomization information, randomized treatment and actual treatments. This listing will incorporate information from the random dataset

provided by Global Randomization Group. An unblinding .csv data set and the corresponding decode .csv data set will be prepared according to MAN-000255. Those datasets will be provided to safety in order to unblind ARGUS database.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. If a snapshot is being taken during the study rather than a database lock at the end of the study, categories should be updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. The final IPD list is used to produce the list of subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided.

10.4 Demographic and Baseline Characteristics

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

A listing of the demographic and baseline characteristics will be reviewed. In addition a listing of medical history will be reviewed.

10.5 Safety Analyses

10.5.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or later will be used to code all adverse events to a system organ class and a preferred term.

The subject incidence of adverse events by treatment group will be summarized for all treatment emergent, serious treatment emergent, treatment related, serious treatment related, those leading to withdrawal of investigational product, severe, life threatening and fatal adverse events.

The severity of each adverse event will be graded using CTCAE version 4.0 criteria (**see Appendix B)**. Subject incidence of treatment emergent events and treatment related treatment emergent events will further be summarized by worst severity grade.

Subject incidence of all treatment emergent, serious treatment emergent, treatment related, serious treatment related, treatment emergent events leading to withdrawal of investigational product, and treatment emergent fatal adverse events will further be tabulated by system organ class and preferred term in descending order of frequency. The above adverse event tables will not be created if two or fewer subjects in the study experience the adverse event.

Details of each adverse event will be reviewed. Listings and/or narratives of any on-study deaths, serious treatment-emergent adverse events, including early withdrawals due to adverse events, also will be reviewed should they occur.

10.5.2 Laboratory Test Results

10.5.2.1 Chemistry and Hematology

Individual chemistry and hematology laboratory data will be reviewed.

Summary of baseline lab value, change from baseline to post dose maximum, time to post-baseline maximum, change from baseline to post- baseline minimum, and the time to post-baseline minimum may also be provided for selected parameters. Shifts in grades based on CTCAE of safety laboratory values between the baseline and the worst on-study value may be tabulated by treatment group for selected parameters given below in Table 3. Unscheduled assessments will be incorporated in the laboratory analyses where possible.

Summaries of the absolute value and/or changes from baseline at each scheduled assessment will be provided for selected hematology analytes including Neutrophils, Basophils, Eosinophils, Lymphocytes, and Monocytes for each treatment group. Plots of the mean values of analytes with 95% confidence intervals over time for each treatment group will also be produced.

10.5.2.2 Urinalysis

Individual urinalysis data will be reviewed.

Blood, protein, glucose and bilirubin will be graded in the following manner: 0=’0 or Trace’, 1=’1+’, 2=’2+’, 3=’3+’, 4=’4+’. The number and percent of subjects by worst post-dose levels will be presented for blood, protein and glucose in the urine.

Microscopic parameters (WBC, RBC, epithelial cells, bacteria, casts, and crystals) will be graded in the following manner: 0=’0-4 none, rare, occasional’, 1=’5-50 moderate, few’, 2=’>50 per high powered field (HPF) many, heavy, too numerous to count’. The

number and percent of subjects in these categories at each scheduled timepoint will be presented.

Summary of baseline lab value, change from baseline to post dose maximum, time to post-baseline maximum, change from baseline to post- baseline minimum, and the time to post-baseline minimum may also be provided for selected parameters in Table 3. Shifts in grades based on CTCAE of safety laboratory values between the baseline and the worst on-study value may be tabulated by treatment group for selected parameters. Summaries of the absolute value and/or changes from baseline at each scheduled assessment will also be provided for specific gravity and pH values. For ketones and urobilinogen, the number and percent of subjects in each of the reported categories will be presented at each scheduled timepoint.

Table 3. Selected Laboratory Parameters

Chemistry	Hematology	Urinalysis
Blood urea nitrogen (BUN) or Urea Glucose Creatinine Carbon Dioxide Bicarbonate Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin (TBIL) Alkaline phosphatase (ALP) Creatine Phosphokinase (CPK)	All hematology tests mentioned in the protocol	Protein

10.5.3 Vital Signs

Vital signs data will be reviewed for each subject. Vital signs will include the following parameters – Systolic BP (mmHg), Diastolic BP (mmHg), Pulse Rate (beats/min), Respiratory Rate (breaths/min), Temperature (C). Depending on the size and scope of the changes, the analyses of vital signs may include summary statistics over time and/or changes from baseline over time by treatment.

10.5.4 Electrocardiograms

All on-study ECG data will be reviewed. Each ECG will include the following measurements: QRS, QT, QTc, RR, and PR intervals. The Bazett's (QTcB) and Fridericia's (QTcF) QT correction will be computed as specified in section 6.

Summaries of baseline value, change from baseline to post dose maximum, time to post-baseline maximum, change from baseline to post- baseline minimum, and the time to post-baseline minimum will be provided for all 12-lead ECG parameters.

Further, subjects' maximum change from baseline in QTcF and QTcB will be categorized in following categories and the number and percentage of subjects in each group will be summarized. Unscheduled assessments will be included in the determination of the maximum change.

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

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

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

The number of subjects in each group will be summarized for each dosing group.
In addition, the relationship between serum concentration of AMG 570 and change from baseline in QTcF and QTcB will be explored graphically; if both QTcF and QTcB exhibit similar relationships, only the QTcF graph will be provided.

10.5.5 Antibody Formation

Anti-AMG 570 binding antibody will be assessed using a validated assay. The incidence of anti-AMG 570 antibodies will be reviewed for each subject. The number and percentage of subjects who have developed anti- AMG 570 antibodies (binding and if positive, neutralizing) at any time, at baseline and during post-baseline visits will be summarized by treatment group.

10.5.6 Exposure to Investigational Product

The quantity of investigational product administered (mg) will be reported in the clinical database. Descriptive statistics may be produced to describe the exposure to investigational product. Details for each AMG 570 administration will be reviewed for every subject. In addition a listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

10.5.7 Exposure to Concomitant Medication

All medication will be coded using the WHO drug dictionary. Summary of concomitant medication use by preferred name will be provided. A subject listing of all prior and concomitant medications will be reviewed.

10.5.8 Subjects With Potential DILI Events

For subjects identified with potential DILI events (including those satisfying Hy's law criteria) during the study, listings of hepatic history, results of additional laboratory tests, vital signs, liver imaging results (if performed), liver biopsy results (if performed), and substance use will be separately provided.

10.6 Pharmacokinetic Analysis

Serum AMG 570 concentrations will be determined using a validated assay.

Actual dosing and sampling time will be used for all calculations.

Individual concentration-time data will be listed and presented graphically. Individual concentration listings will report concentrations using nominal time. Descriptive statistics for PK concentrations will be provided by treatment group and time. Mean concentration-time profiles for each dose will be provided.

The following pharmacokinetic parameters will be calculated by Clinial Pharmacology, Modeling and Simulation (CPMS) group: total systemic clearance (CL), maximum observed concentration [C_{max}], time at C_{max} [t_{max},], and area under the concentration- time curve from time zero to time of last quantifiable concentration [$AUC_{0\text{-}last}$] using non-compartmental methods. Terminal half-life [$t_{1/2}$] and area under the concentration-time curve from zero to infinite time [$AUC_{0\text{-}inf}$] may or may not be calculated for all subjects; this would be assessed based on the subject profiles. PK parameters will be summarized for each dose using descriptive statistics.

10.7 Pharmacodynamic Analysis

10.7.1 Humoral Immune Status Stopping Rules

Individual subjects that satisfy the Humoral Immune Status Stopping Rules stated in Section 6.2.1.3 of the study protocol will be listed. The listing will include peripheral blood absolute CD19+ B cell count and serum IgG levels at all visits up to the end of study visit for these subjects.

10.7.2 T Cells, NK Cells, B Cells and B Cell Subsets

A dual-platform approach will be used to measure circulating T cells, NK cells and B cells. A custom, validated immunophenotyping assay will be used to measure B cell subsets. The end points include absolute counts and percentages (of lymphocytes) for CD3+ T cells, CD16/56+ NK cells, CD19+ B cells, and absolute counts and percentages (of B cells) for naïve and memory CD19+ B cells. For these endpoints, absolute values and percentages as well as the corresponding change from baseline and fold change from baseline will be summarized descriptively at each scheduled visit for each treatment group. For these end points, the individual time course and the mean values with 95% confidence intervals over time for each treatment group plots will be produced. Plots will be designed in collaboration with CBDD. Data may be reviewed by subject if deemed necessary.

A listing of subjects with B cell counts <107 cells/uL or serum IgG value < 639 mg/dl at any time during the study will be provided. For the primary analysis, the listing will include B cell counts and IgG values at all visits up to the end of study visit. After the completion of the trial, this listing will be updated if there is an additional safety follow-up (up to 12 months) after the end of study visit for any of the subjects who had low B cell counts at the end of study visit as stated in Section 3.5.1 and Section 7.1 of the protocol.

A mixed effects repeated measure analysis of variance/covariance models will be applied to selected end points (absolute B cell counts and percentages, naïve B cell counts and percentages, memory B cell counts and percentages) to evaluate the difference between a dose group and placebo over time. For these analyses the dependent continuous variable will be the endpoint response and independent variables will include subject, time, dose group, and the interaction between time and dose groups. Both time and dose will be considered nominal factors, and subject will be treated as a random factor. Baseline is included as a covariate in the model to adjust for baseline differences. A transformation to the data may be applied to attain homogenous variance and adjust for skewness prior to fitting the model. The data will be back

transformed for result reporting. The dose-by-time longitudinal least square means will be estimated and reported with corresponding 95% confidence intervals.

Additional analysis will be described in the Clinical Biomarkers Discovery and Development (CBDD) Biomarker Data Analysis Plan (BDAP).

10.7.3 Free B7RP-1, Total B7RP-1 and B7RP-1 Receptor Occupancy

A Immunophenotyping and receptor occupancy assay (IPRO) will be used to measure free B7RP-1 and total B7RP-1 on circulating Total B cells, memory B cells, and monocytes. B7RP-1 receptor occupancy (RO) will be calculated from the free B7RP-1 and total B7RP-1 measurements as defined in section 6. The end points associated with receptor occupancy are peripheral blood free B7RP-1 MFI on Total B cells, memory B cells, and monocytes, maximum saturated free B7RP-1 MFI on Total B cells, memory B cells, and monocytes, peripheral blood total B7RP-1 MFI on Total B cells, memory B cells, and monocytes and peripheral blood B7RP-1 receptor occupancy on Total B cells, memory B cells, and monocytes.

For each endpoint, absolute values as well as the corresponding change from baseline and fold change from baseline will be summarized descriptively at each scheduled visit for each treatment group. Further, the individual time course and the mean values with 95% confidence intervals over time for each treatment group plots will be produced. Plots will be designed in collaboration with CBDD. Data may be reviewed by subject if deemed necessary.

A mixed effects repeated measure analysis of variance/covariance models will be applied for RO to evaluate the difference between each dose group and placebo over time. The dependent continuous variable will be the RO and independent variables will include subject, time, dose group, and the interaction between time and dose groups. Both time and dose will be considered nominal factors, and subject will be treated as a random factor. A transformation to the data may be applied to attain homogenous variance and adjust for skewness prior to fitting the model. The data will be back transformed for result reporting. The dose-by-time longitudinal least square means will be estimated and reported with corresponding 95% confidence intervals.

Additional analysis will be described in the CBDD BDAP.

10.7.4 [redacted] and Serum IgG and IgM Levels

Absolute values as well as change from baseline and fold change from baseline (for selected endpoints) will be summarized descriptively at each scheduled visit. Data may

be reviewed by subject if deemed necessary. Additional analysis of the [redacted] IgG and IgM levels will be described in the CBDD BDAP.

10.8 PK/ PD Analysis

The relationship between PK and B7RP-1 occupancy, [redacted] and percentage and/or absolute counts of naïve and memory B cells following single SC doses of AMG 570 may be explored and reported separately by CPMS group.

11. Changes From Protocol-Specified Analyses

During the initial development of this document, it was realized that there are protocol-specified analyses that cannot be implemented/performed and the protocol is not required to be amended. These changes are documented below. These changes will also be documented in the Clinical Study Report.

Protocol specifies that the subject incidence of significant treatment emergent adverse by treatment group will be summarized. However, it is not possible to prospectively define such significant events since this is a study of healthy subjects. Hence, this analysis is not planned in the SAP.

The protocol mentions that incidence of anti-AMG 570 antibodies will be listed for each subject. Although this subject-level listing will be reviewed as part of ongoing data review, it will not be provided in the clinical study report as per the guidance across Amgen studies to include only critical subject-level data listings in the clinical study report.

12. Literature Citations / References

13. Prioritization Of Analyses

Tables to precede listings

14. Data Not Covered By This Plan

Exploratory data not included in this plan may be analyzed at a later date or may be analyzed by a different Amgen Department.

15. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures

Imputation Rules for Partial or Missing Stop Dates

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

Imputation Rules for Partial or Missing Start Dates

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

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Schedule of Assessments

AMG 570 Schedule of Assessments

Activity	Screen	Treatment and Evaluation (each dosing session)																		EOS[1]
Month																~1m			~2m	3.5m
Study Day	Screening[8]	Day -1	Day 1					Day 2	Day 3	Day 4	Day 6[2]	Day 8	Day 11[2]	Day 15	Day 22[2]	Day 29	Day 43	Day 57	Day 71	Day 105
Window	-42 to -1				10m (+/-)	15m (+/-)	30m (+/-)	30m (+/-)	60m (+/-)	6h (+/-)	1d (+/-)	1d (+/-)	1d (+/-)	1d (+/-)	2d (+/-)	2d (+/-)	4d (+/-)	4d (+/-)	4d (+/-)	4d (+/-)
Relative to Dosing(h)			Pre	0	0.5	6	12	24	48	72	120	168	240	336	504	672	1008	1344	1680	2496
General Assessment																				
ICF	X																			
Eligibility	X																			
Medical/Med/Drug/Alcohol History	X																			
Demographics	X																			
BMI (Ht & Wt)	X																			
General Safety Assessments																				
Physical Exam [2]	X	X							X							X		X		X
Vitals	X	X	X	X	X	X	X	X	X			X		X		X		X		X
ECG[3]	X	X				X	X		X			X				X		X		X
AEs & Con. Meds			←																	
SAE	←																			
Lab Assessments																				
Drug/ Alcohol/Cotinine screen	X	X																		
HIV, HepC, HepB	X																			
Hem/Chem/Urinalysis[4]	X	X							X							X		X		X
Pregnancy Test	X	X																		X
FSH/Estradiol	X																			
Dosing																				
Treatment Assignment		X																		
AMG 570 or Placebo				X																

Page 1 of 2

Footnotes defined on the last page of this table.

AMG 570 Schedule of Assessments

Activity	Screen	Treatment and Evaluation (each dosing session)																		EOS[1]
Month																~1m			~2m	3.5m
Study Day	Screening	Day -1	Day 1					Day 2	Day 3	Day 4	Day 6	Day 8	Day 11	Day 15	Day 22	Day 29	Day 43	Day 57	Day 71	Day 105
Window	-42 to -1				10m (+/-)	15m (+/-)	30m (+/-)	30m (+/-)	60m (+/-)	6h (+/-)	1d (+/-)	1d (+/-)	1d (+/-)	1d (+/-)	2d (+/-)	2d (+/-)	4d (+/-)	4d (+/-)	4d (+/-)	4d (+/-)
Relative to Dosing(h)			Pre	0	0.5	6	12	24	48	72	120	168	240	336	504	672	1008	1344	1680	2496
PK Assessments of AMG 570																				
Cohort 1 to 6			X				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker & Immunological Assessments																				
Immunophenotyping and Receptor Occupancy (IP & RO) assays[5]	X		X									X				X		X		X
ADA			X													X		X		X
IgG and IgM serum	X		X									X				X		X		X
BAFF serum levels			X									X				X		X		X
Exploratory Biomarkers[6]			X									X				X		X		X
Pharmacogenetic																				
Blood for cell pellets[7]			X																	

Page 2 of 2

[1] If a subject's CD3-CD19+ B cell counts are < 107 cells/uL (the lower limit of normal for healthy volunteers, the subject will return for further testing of B cell counts every 3 months until the subject has B cell counts ≥ 107 cells/uL. Follow-up visits for B cell counts will continue every 3 months, for up to 12 months after the end of study.
[2] A complete physical will be performed at screening and EOS. A brief physical will be performed at all other timepoints unless required for evaluation of AEs.
[3] On day -1 baseline, three sets of triplicate baseline ECGs will be collected ≥ 30 minutes apart and at other time-points single triplicate ECGs will be collected, approximately 60 seconds apart.
[4] All Subjects must fast from all food and drink (except water) for at least 8 hours prior to any clinical lab evaluation.
[5] The AMG 570 IPRO assay will measure absolute counts for CD3+ T cells, CD16/56+ NK cells, CD19+ B cells as well as: 1) naïve B cell % of B cells and counts; 2) memory B cell % of B cells and counts; 3) free B7RP-1 MFI (or MESF) on memory B cells and: 4) total B7RP-1 MFI (or MESF) on memory B cells. Receptor occupancy will be calculated from the measurements of free and total B7RP-1.
[6].Exploratory biomarkers will include collection of serum, plasma and PAX gene RNA for future use.
[7] Blood for cell pellet sample will be obtained from the exploratory biomarker sample
[8] Subjects who require vaccination must receive vaccination(s) at least 30 days prior to receiving IP (tetanus booster and flu vaccinations may be administered by the investigator site during the screening window) Seasonal influenze vaccine need only be administered during influenza season (October through May)

.

Appendix B. Reference Values/Toxicity Grades

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used and is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm