STATISTICAL ANALYSIS PLAN

Title: A Randomized, Double Blind Placebo Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Multiple Ascending Subcutaneous Doses of AMG 570 in Subjects With Rheumatoid Arthritis

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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	12JUN2017	
[Amendment 1 (v2.0)]	13AUG2019	Changes in the protocol amendment related to addition of Cohort 4 Removal of unnecessary listings as per recent process

Note: Please see the Appendix C for detailed summary of changes and rationale for changes to Amendment 1 (change-Memo).

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Table of Abbreviations

Abbreviation/Acronym	Definition
AE	Adverse event
ALP	Alkaline Phosphate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration
BAFF	**B cell activating factor**
B7RP-1	B 7 related protein 1, aka ICOSL
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C_{max}	Maximum observed serum concentration
CPMS	Clinical Pharmacology, Modeling and Simulation
CTCAE	Common terminology criteria for adverse events
DBP	Diastolic Blood Pressure
DILI	**Drug-induced liver injury**
DLRM	Dose Level Review Meeting
DMP	Data management plan
CRP	**C-Reactive Protein**
DAS	**Disease Activity Score**
ESR	**Erythrocyte Sedimentation Rate**
eCRF	Electronic case report form
ECG	Electrocardiogram
EOS	End of study
GBS	Global Biostatistical Science
GGT	Gamma Glutamyl Transferase
HR	Heart Rate
ICOSL	**Inducible co-stimulator ligand**
IP	Investigational Product, in this double-blind study, investigational product may be AMG 570 or placebo
IPD	Important Protocol Deviation

Abbreviation/Acronym	**Definition**
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MAD	Multiple Ascending Dose
NK Cells	Natural Killer Cells
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKDM	Pharmacokinetics and drug metabolism
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
Q1	**First quartile**
Q3	**Third quartile**
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
QTc	QT interval corrected for heart rate using accepted methodology
QTcB	Bazett-corrected QT interval
QTcF	Fridericia-corrected QT interval
RA	**Rheumatoid arthritis**
RBC	Red Blood Cells
RO	**Receptor Occupancy**
SAE	Serious Adverse event
SAP	Statistical Analysis plan
SBP	Systolic Blood Pressure
SC	Subcutaneous
SOP	Standard Operating Procedure
T_{max}	Time to C_{max}
TEAE	Treatment Emergent Adverse Events
Tfh	**T follicular helper**
VAS	Visual Analogue Scale
WBC	White Blood Cells

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 for AMG 570 study 20150196 dated **08 June 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 **Amgen** Global Biostatistical Sciences (GBS) unless otherwise specified.

2. Objectives

2.1 Primary

To evaluate the safety and tolerability of AMG 570 following multiple dose subcutaneous (SC) administration in subjects with rheumatoid arthritis (RA).

2.2 Secondary

To characterize the pharmacokinetic profile of AMG 570 following multiple dose SC administration in subjects with RA.

2.3 Exploratory

- To characterize the pharmacodynamic effects of multiple subcutaneous doses of AMG 570 in subjects with RA on peripheral blood B cell levels (total B cells as well as naive, memory subpopulations), peripheral blood ICOSL Receptor Occupancy on B cells, serum BAFF levels , serum Immunoglobulin levels**, plasma cells and circulating T follicular helper (Tfh) cells.**
- To characterize pharmacokinetic and pharmacodynamic relationships after multiple subcutaneous doses of AMG 570 in subjects with RA.
- To characterize effects of multiple subcutaneous doses of AMG 570 on clinical and serologic indices of RA disease activity in subjects with RA.
- To evaluate the immunogenicity of multiple subcutaneous doses of AMG 570 in subjects RA

3. Study Overview

3.1 Study Design

This is a randomized, placebo-controlled, double-blind, MAD study in subjects with RA. The study consists of **4** 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	Dosing interval	Number of planned doses	N(active:placebo)
1	70	SC	Q 2 weeks	6	8 (6:2)
2	140	SC	Q 2 weeks	6	8 (6:2)
3	210	SC	Q 2 weeks	6	8 (6:2)
4	**420**	**SC**	**Q 2 weeks**	**6**	**8 (6:2)**

The overall study design is described in the section 3.1 of the protocol. The study endpoints are defined in Section 4.

3.2 Sample Size

Approximately **32** RA patients will be enrolled into **4** cohorts with 6 subjects randomized to AMG570 and 2 subjects randomized to 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 assuming a true incidence rate of 25% and a 74% chance of at least one subject experiencing an adverse event assuming 20% true incidence rate. With a total of **24** subjects expected to receive AMG 570 across all **4** cohorts, there is a **21**% chance of at least 1 subject experiencing an adverse event assuming a true incidence rate of 1% and the chance of at least 1 subject experiencing an adverse event increases to **71**% and **92**% assuming a true incidence rate of 5% and 10%, respectively.

4. Study Endpoints

4.1 Primary Endpoint

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

4.2 Secondary Endpoint(s)

- AMG 570 serum PK profiles after multiple dose administrations. PK parameters will include, but are not limited to, maximum observed concentration [Cmax], area under the concentration-time curve [AUC] after the first and the last doses, and the accumulation ratio.

4.3 Exploratory Endpoint(s)

- Peripheral blood ICOSL receptor occupancy
- Baseline levels, post-dose levels and change from baseline in peripheral blood percentage and absolute counts of total T cells, B cells and NK cells
- Baseline levels, post-dose levels and change from baseline in peripheral blood percentage and absolute counts of naive and memory B cells (naive = CD19+IgD+CD27-, memory = CD19+IgD-CD27+)
- Baseline levels, post-dose levels and change from baseline in circulating Plasma cells by gene signature
- Baseline levels, post-dose levels and change from baseline in circulating Tfh by **flow cytometry and** gene signature
- Baseline levels, post-dose levels and change from baseline in serum Immunoglobulin M, Immunoglobulin G and Immunoglobulin A

- Baseline levels, post-dose levels and change from baseline in serum BAFF
- Baseline levels, post-dose levels and change from baseline in serum CRP, ESR, IgG+ Rheumatoid Factor, IgM+ Rheumatoid Factor and anti-citrullinated protein antibody
- Changes from baseline over time in the disease activity score based on 28 joints (DAS 28-CRP)
- Changes from baseline over time in Patient Global Assessment of Disease Activity
- Changes from baseline over time in Physician Global Assessment of Disease Activity
- Incidence of anti-AMG 570 binding and neutralizing antibodies

5. Hypotheses and/or Estimations

Multiple SC dose administration of AMG 570 will have acceptable safety and tolerability profiles in RA subjects within the proposed dose range (70 to **420** mg AMG 570)

6. Definitions

6.1 General Definitions

Accumulation Ratio

Accumulation Ratio is the ratio of AUC after the last dosing interval divided by AUC after the first dosing interval

Age at Enrollment

Subject age at enrollment will be collected in years in the clinical database

$AUC_{0\ last}$

Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration.

Baseline

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

Baseline ECG

The baseline ECG is defined as the average of the mean of the triplicates at Day **1 pre-dose**; 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:

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

BMI

Subject's BMI will be derived in kg/m^2 in the clinical database

Change From Baseline

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

C_{max}

Maximum observed serum concentration.

ECG analysis value

ECGs will be performed in triplicate, approximately 1 minute apart, at time points specified in the Schedule of Assessments. On **Day 1 pre-dose**, three sets of triplicate ECGs will be collected, with each set being ≥ 30 minutes apart (ie, total of 9 ECGs). At other time points single triplicate ECGs will be collected. The mean value of each 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 time point. Further, unscheduled ECG measurements taken up to 5 minute after the last assessment of a triplicate at a time point will be included in the mean for that time point.

End of IP Admin Date

End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of IP eCRF.

End-of-Study

Primary Completion: the date 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 Study: the time when the last subject has completed either the EOS visit or the last safety follow-up visit (if applicable). The EOS for each cohort may be prolonged pending treatment- emergent data.

Enrollment Date

Enrollment Date is defined as the randomization date and will be collected on the enrollment eCRF.

Dose administered

For AMG 570 subjects, dose administered (mg) is the quantity administered (mg) as recorded on IP administration eCRF. For placebo subjects, the dose administered will be 0 mg. The actual treatment assignment (AMG 570 versus placebo) will be determined based on package lot numbers entered on IP administration eCRF and concentration of active drug in those lots as per the information in manufacturing lot file.

Fold change from Baseline

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

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT and RR interval ($QTcF=QT/(RR/1000)^{0.33}$).

Investigational Product

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

Last IP Dose Date

Last IP Dose Date for each subject is defined as the latest date IP is administered

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

Peripheral blood ICOSL receptor occupancy (RO) **(MFI-based)**

RO on total B cells, memory B cells, and monocytes will be calculated as follows:

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

Where

background subtracted free ICOSL = free ICOSL – Maximally saturated free ICOSL
background subtracted total ICOSL = total ICOSL – **background subtraction factor**

Background subtraction factor is 171, 208 and 96 for total B cells, memory B cells and monocytes respectively.

RO is 0 at baseline.

Randomization Date

Randomization Date is defined as the date subject was allocated to a randomization number and assigned to either AMG 570 or placebo group.

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 as Day -1.

Subject-level End of Study (EOS) Date

End of study for each subject is defined as the date the subject completed the EOS visit. The date will be recorded on the End of Study eCRF.

Treatment-emergent adverse event

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product (as determined by the flag indicating if the adverse event started prior to the first dose or not on the Events eCRF) and up to the end of study **(ie, EOS visit)**.

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 and marked accordingly on the Events eCRF.

7. Analysis Subsets

For all analyses, subjects will be analyzed according to the treatment they received.

7.1 Safety Analysis Set

The safety analysis set will include all randomized subjects who received at least one dose of AMG 570/placebo.

7.2 Pharmacokinetic Concentration Analysis Set

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

7.3 Pharmacokinetic Parameter Analysis Set

The pharmacokinetic (PK) parameter analysis set will contain all randomized subjects who received AMG 570 and for whom PK parameters can be adequately estimated

7.4 Pharmacodynamic Analysis Set

The pharmacodynamic (PD) analysis set will contain all randomized subjects who received at least 1 dose of investigational product (AMG 570 or Placebo) and for whom at least 1 PD parameter has baseline and at least 1 post baseline measurement available.

8. Planned Analyses

8.1 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 all 8 subjects have been enrolled in each cohort and at least 6 of them have completed the day 29 visit. Details of DLRMs are given in section 6.2.1.2 of the protocol.

8.2 Primary Analysis

The primary analysis will be performed when all subjects have completed the study ie, the end of study (EOS) visit.

8.3 Final Analysis

Primary analysis is the final analysis for the study ie, no analysis will be done after the primary analysis.

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

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

9.3 Handling of Missing and Incomplete Data

The following imputation of missing values will be done:

- Incomplete adverse event dates 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

Any source that may introduce the bias in the analysis eg, important protocol deviations, imbalance in baseline characteristics among treatment groups, subject dropout for study or treatment related reasons, nonrandom or informative censoring will be noted in the clinical study report.

9.5 Outliers

Details of detecting outliers can be found in the DMP or other data management documents. 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 version 9.4 or later.

10. Statistical Methods of Analysis

10.1 General Considerations

Descriptive statistics will be provided for selected **subject disposition,** demographics, safety, immunogenicity, PK, PD, and biomarker data. Descriptive statistics on continuous measurements will include means, medians, **Q1, Q3,** standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Data will summarized by treatment and by scheduled timepoint unless specified otherwise. 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.

The number and percent of subjects enrolled will be tabulated by study site.

A summary noting inclusion in each analysis subset will be provided for all subjects enrolled. A subject listing will be provided for randomization information, randomized treatment and actual treatments.

10.3 Important Protocol Deviations

The final list of important protocol deviations (IPDs) will be used to produce the listing 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 (age, age groups [**18-64 years, 65-74 years and >=75 years**], sex, race, and ethnicity) and baseline characteristics (height, weight, and BMI) will be summarized by treatment group and overall. If multiple races have been reported for a subject, the subject will be categorized as multiple races as well as by the combination of races.

10.5 Safety Analyses

10.5.1 Adverse Events and Disease Related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **22.0** or later will be used to code all events categorized as adverse events (AEs) to a system organ class and a preferred term.

The subject incidence of AEs by treatment group will be summarized for all treatment-emergent AEs, serious treatment-emergent AEs, treatment related AEs, serious treatment related AEs, AEs leading to withdrawal of investigational product, **and** fatal AEs.

The severity of each adverse event will be graded using CTCAE version 4.0 or later version (Refer - 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 AEs, serious treatment-emergent AEs,Treatment-related AEs, Serious treatment-related AEs, those leading to withdrawal of investigational product, and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency.

10.5.2 Laboratory Test Results

10.5.2.1 Chemistry and Hematology

Parameters that will be collected are listed in Table 2.

Unscheduled assessments will be incorporated in the laboratory analyses where possible.

For the parameters that are bolded in Table 2, 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 will be provided**. Further,** shifts in grades based on CTCAE version 4.0 or later between the baseline and the worst on-study value will be **provided for the parameters where CTCAE grading is available .**

10.5.2.2 Urinalysis

Parameters that will be collected are listed in Table 2.

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 these analytes.

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 many, heavy, too numerous to count'. The number and percent of subjects in these categories at each scheduled time point will be presented. Summary statistics and change from baseline over time will be provided for Specific gravity, **and** pH values. **Descriptive statistics will be provided for** Urobilinogen.

Table 2. List of Laboratory Parameters

Chemistry	Hematology	Urinalysis
Alanine aminotransferase (ALT)	**Erythrocyte Sedimentation Rate (ESR)**	Specific gravity
Albumin	**Hemoglobin**	pH
Alkaline phosphatase	**Hematocrit**	Blood
Aspartate aminotransferase (AST)	**Mean corpuscular volume (MCV)**	Protein
Bicarbonate (HCO3) or Carbon Dioxide	**Mean Corpuscular Hemoglobin (MCH)**	Glucose
Bilirubin	**Mean Corpuscular Hemoglobin Conc (MCHC)**	Bilirubin
• Total	**Red Blood Cell count**	Urobilinogen
• Direct	**Platelets**	Microscopic exam White blood cells
Blood urea nitrogen or Urea	**Reticulocyte count**	• Red blood cells
Calcium	**White blood cell count**	• Epithelial cells
Chloride	**White blood cell Differential (in absolute cell numbers)**	• Bacteria
Cholesterol	• **Total neutrophils**	• Casts
Creatinine	• **Eosinophils**	• Crystals
Creatine phosphokinase (CPK)	• **Basophils**	
Gamma-glutamyl transferase (GGT)	• **Lymphocytes**	
Glucose	• **Monocytes**	
High-density lipoprotein		
Magnesium		
Phosphorus		
Potassium		
Sodium		
Total protein		
Triglycerides		
Uric acid		
Hemoglobin A1C**		
CRP		

10.5.3 Vital Signs

The summary statistics over time and/or changes from baseline over time by treatment will be produced for SBP, DBP, pulse rate, HR and temperature.

10.5.4 Electrocardiogram (ECG)

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 of this document.

Summaries of baseline value, **maximum post-baseline and change from baseline to post – baseline maximum** by treatment group 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. Unscheduled assessments will be included in the determination of the maximum post baseline value

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

In addition, the relationship between serum concentration of AMG 570 and change from baseline in QTcF and QTcB will be explored graphically.

10.5.5 Antibody Formation

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

Descriptive statistics will be produced to describe the exposure to **AMG 570** by treatment group.

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

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 Analysis of Exploratory Efficacy Endpoints

Safety analyses set will be used for the analy**s**es described in this section

10.6.1 Disease Activity Score Based on 28 Joints (DAS 28-CRP)

The DAS28-CRP is a composite score that is based on 28-joint count (using tender and swollen joints), CRP **(mg/L)** , and Patient Global Assessment of Disease Activity. Calculation of the DAS28-CRP score is as follows:

DAS28-CRP = 0.56 √TJC28 + 0.28 √SJC28 + 0.36 x ln (CRP + 1) + 0.014 x Patient Global Assessment of Disease Activity score + 0.96

Where TJC28 and SJC28 represent the tender and swollen 28 joint counts, respectively. The 28 joint counts includes 10 proximal interphalangeal, 10 metacarpophalangeal, 2 wrist, 2 elbow, 2 shoulder, and 2 knee joints.

To calculate the swollen joint counts at least half of those joints listed above (ie, 14 joints) need to be evaluated ie, have an entry of (0 or 1) where 0 is none (no swelling or effusion) and 1 is positive (detectable effusion or synovial thickening) ; otherwise the SJC28 will be missing. If all joints are evaluated, then SJC28 is the number of joints with 1. If some joints are missing, but still have at least 14 joints evaluated, then SJC28 is (number of joints with (1) / number of evaluated joints) * 28. Similarly, TJC28 will be calculated. If any of TJC28, SJC28, Patient Global Assessment of Disease Activity score or CRP value is missing, then DAS28-CRP will be

missing. Summary statistics of DAS28-CRP and change from baseline in DAS28-CRP will be provided at all applicable time-points.

10.6.2 Patient Global Assessment of Disease Activity

The patient will rate the patient's arthritis status by marking an "X" on the 100 mm horizontal line where 0 is no activity at all and 100 is worst activity imaginable. The score will be documented on the eCRF. Summary statistics of the score and change from baseline in the score will be provided at all evaluable time-points.

10.6.3 Physician Global Assessment of Disease Activity

The treating physician will rate the patient's disease activity by marking an "X" on the 100 mm horizontal line where 0 is no activity at all and 100 is worst activity imaginable. The score will be documented on the eCRF. Summary statistics of the score and change from baseline in the score will be provided at all evaluable time-points.

10.6.4 Disability Index of the Health Assessment Question(HAQ-DI)

HAQ is used to assess a subject's physical function or disability according to the subject. It includes a Disability Index (DI) and a VAS for pain. Disability Index include 8 categories (dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and activities ie,errands or chores). Responses for each category range from 0 (without any difficulty) to 3 (unable to do). The scoring algorithm is as follows:

- Obtain the maximum score reported for any component question of the above 8 categories (the highest score reported for any component question of the eight categories determines the score for that category);
- If either devices or help from another person are checked for a category, then the category score is set to "2", but if the subject's highest score for that category is a "2", it remains a "2", and if a "3", it remains a "3". Please see Table 3 for the companion devices for calculating the HAQ-DI category scores (the eighth category —Activities is not listed in Table 3 due to lack of questions regarding use of devices).
- A global DI score is the mean of the nonmissing category scores. If there are more than 2 categories with missing responses, a DI score will be set to missing.

Table 3. Companion Devices/Help Items for HAQ-DI Categories

HAQ-DI Category	Companion Device Item
Dressing & Grooming	Devices used for dressing (Button hook, zipper pull, long-handled shoe horn, etc.)
Arising	Special or built up chair
Eating	Built up or special utensils
Walking	Cane, Walker, Crutches, Wheelchair
Hygiene	Raised toilet seat, Bathtub seat, Bathtub bar, Long-handled appliances in bathroom
Reach	Long-handled appliances for reach
Grip	Jar opener (for jars previously opened)

Descriptive statistics for HAQ-DI global score and change from baseline in the score will be provided at each evaluable timepoint.

The pain VAS scale measures the distance (D in cm) from the left side of the line to the mark on a 100 mm scale where 0 is no pain and 100 is severe pain. Descriptive statistics for pain score and change from baseline in the score will be provided at each evaluable timepoint.

10.7 Pharmacokinetic Analysis

Pharmacokinetics analyses will be performed by Clinial Pharmacology, Modeling and Simulation (CPMS) group. Serum AMG 570 concentrations will be determined using a validated assay. Individual serum concentration-time plots for AMG 570 will be presented for each subject as well as mean concentration-time plots for each treatment. Descriptive statistics for PK concentrations will be provided by treatment group and time. Mean concentration-time profiles for each dose will be provided. Pharmacokinetic parameters may include, but are not limited to, maximum observed concentration [Cmax] time at Cmax [tmax], area under the concentration-time curve [AUC], after the first and the last dose, in addition to the accumulation ratio.Parameters will be calculated using non-compartmental methods. Actual dosing and sampling times will be used for calculation of individual PK parameters. Summary statistics will be generated for each PK parameter. Additional analyses using compartmental methods or population PK analysis may be performed.

10.8 Pharmacodynamic Analysis

The endpoints such as a peripheral blood ICOSL receptor occupancy, percentage and absolute counts of total T cells, B cells and NK cells, percentage and absolute counts of

naive and memory B cells (naive = CD19+IgD+CD27-, memory = CD19+IgD-CD27+), serum Immunoglobulin M, Immunoglobulin G and Immunoglobulin A, serum BAFF, serum CRP, ESR, IgG+ Rheumatoid Factor, IgM+ Rheumatoid Factor, IgA+ Rheumatoid Factor and anti-citrullinated protein antibody will be summarized by treatment group using descriptive statistics at each visit. For each end point,the change from baseline, **percent change from baseline,** and/or fold change from baseline will be summarized by treatment using descriptive statistics at post-baseline visit. **For selected analytes, plots of selected summary statistics (eg, mean, mean change, mean fold change or mean percent change) over time may be plotted by treatment group as deemed necessary.**

11. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

12. Prioritization of Analyses

Tables to precede listings.

13. 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.

14. Appendices

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

Imputation Rules for Partial or Missing Stop Dates

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

		Stop Date						
		Complete: yyyymmdd		**Partial: yyyymm**		**Partial: yyyy**		
Start Date		**< 1st Dose**	**≥ 1st Dose**	**< 1st Dose yyyymm**	**≥ 1st Dose yyyymm**	**< 1st 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: For 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.

Appendix B. Reference Values/Toxicity Grades

The Common Terminology Criteria for Adverse Events (CTCAE) v4.0 is available at the following link:

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

Appendix C. Summary of Changes and Rationale for Changes to the SAP Amendement 1

The statistical analysis plan for this study was amended to reflect the changes in recent protocol amendment 3.

Editorial changes and minor clarifications were also implemented throughout the document.

Description of Changes

Global

- Header date was replaced with 11 July 2019.
- Header version number was replaced with Version 2.0.
- Changes related to addition of Cohort 4
- Removal of unnecessary listings as per recent process

Table of Abbreviations

Added below Abbreviations

BAFF	B cell activating factor
DILI	Drug-induced liver injury
CRP	C-Reactive Protein
DAS	Disease Activity Score
ESR	Erythrocyte Sedimentation Rate
ICOSL	Inducible co-stimulator ligand
Q1	First quartile
Q3	Third quartile
RA	Rheumatoid arthritis
RO	Receptor Occupancy
Tfh	T follicular helper

1. INTRODUCTION

Replaced: dated 13 November 2017 with amendment 3 dated 08 June 2018.

3. Study Overview

3.1 Study Design

Added: Cohort 4 SC 420 mg.

Table 1 Dose Levels

Cohort #	Planned Dose (mg)	Route	Dosing interval	Number of planned doses	N(active:placebo)
4	420	SC	Q 2 weeks	6	8 (6:2)

Reason for change: Updates as per change in the protocol amendment 3.

3.2 Sample Size

Added:

Approximately 32 RA patients will be enrolled into 4 cohorts with 6 subjects randomized to AMG 570 and 2 randomized to 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 assuming a true incidence rate of 25% and a 74% chance of at least one subject experiencing an adverse event assuming 20% true incidence rate. With a total of 24 subjects expected to receive AMG 570 across all 4 cohorts, there is a 21% chance of at least 1 subject experiencing an adverse event assuming a true incidence rate of 1% and the chance of at least 1 subject experiencing an adverse event increases to 71% and 92% assuming a true incidence rate of 5% and 10%, respectively.

Deleted:

Approximately 24 RA patients will be enrolled into 3 cohorts with 6 active and 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 assuming a true incidence rate of 25% and a 74% chance of at least one subject experiencing an adverse event assuming 20% true incidence rate. With a total of 18 subjects expected to receive AMG 570 across all 3 cohorts, there is a 17% chance of at least 1 subject experiencing an adverse event assuming a true incidence rate of 1% and the chance of at least 1 subject experiencing an adverse event increases to 60% and 85% assuming a true incidence rate of 5% and 10%, respectively.

Reason for change: As per protocol amendment 3, 4th cohort added and number of subjects increased from 24 to 32.

4. Study Endpoints

Minor changes to exploratory endpoints to reflect changes in the protocol amendment

5. Hypotheses And/Or Estimates

Added: 420 mg.

Reason for change: To reflect changes in protocol amendment 3.

6. Definitions

Added:

Dose administered

For AMG 570 subjects, dose administered (mg) is the quantity administered (mg) as recorded on IP administration eCRF. For placebo subjects, the dose administered will be 0 mg. The actual treatment assignment (AMG 570 versus placebo) will be determined based on package lot numbers entered on IP administration eCRF and concentration of active drug in those lots as per the information in manufacturing lot file.

For Peripheral blood ICOSL receptor occupancy, added MFI-based in the definition to indicate that calculations are based on MFI method. Further, added MFI-based background subtraction factors for Peripheral blood ICOSL receptor occupancy on total B cells, memory B cells, and monocytes.

Replaced:

For ECG analysis value, the baseline is changed to Day 1 pre-dose instead of Day -1 as per the protocol.

Added sections:

Added section 8.2: Primary Analyses: The primary analysis will be performed when all subjects have completed the study ie, the end of study (EOS) visit.

Added section 8.3: Final Analysis: Primary analysis is the final analysis for the study ie, no analysis will be done after the primary analysis.

10.1 Replaced General Principles with General Considerations

Added: Subject disposition, Q1 and Q3 in the following paragraph.

Descriptive statistics will be provided for selected subject disposition, demographics, safety, immunogenicity, PK, PD, and biomarker data. Descriptive statistics on continuous measurements will include means, medians, Q1, Q3, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages.

Added:

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.

10.4 Demographic and Baseline Characteristics

Modified the age group categories to 18-64 years, 65-74 years and >=75 years as per new EU regulatory requirements.

10.5.1 Adverse Events and Disease Related Events

Replaced: MedDRA version 19.1 with MedDRA version 22.0

Deleted: adverse event tables will not be created if two or fewer subjects in the study experience the event.

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

10.5.2.1 Chemistry and Hematology

Deleted:

Individual Chemistry and Hematology laboratory data will be listed. Values outside the normal laboratory reference ranges will be flagged as high or low.

Replaced:

"Shifts in grades based on CTCAE version 4.0 or later of safety laboratory values between the baseline and the worst on-study value will be tabulated by treatment group" replaced as follows

"Shifts in grades based on CTCAE version 4.0 or later between the baseline and the worst on-study value will be provided for the parameters where CTCAE grading is available."

Deleted following analysis as it is not value-added as confirmed by EDL and it is not mentioned in the protocol

Plots of the mean values of analytes with 95% confidence intervals over time for each treatment group may also be produced for selected analytes.

10.5.2.2 Urinalysis

Deleted:

Individual urinalysis data will be listed.

Added:

Descriptive statistics will be provided for Urobilinogen.
Table 2 List of Laboratory Parameters:

Deleted heading “Local Laboratory”

Added below parameters to reflect changes in protocol amendment 3:

CRP under Chemistry, and Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Conc (MCHC) Red Blood Cell count and Reticulocyte count under hematology

Deleted text “(performed at discretion of investigator or designee)” at Microscopic exam under Urinalysis

10.5.3 Vital signs

Deleted: vital signs data listing will be provided.

Physical Measurement section deleted

10.5.4 Electrocardiogram (ECG)

Deleted following statistics to match with standard summary table shell for ECG data: 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.

10.5.5 Antibody Formation

Deleted: A listing will be provided for subjects who have developed anti AMG570 antibodies.

10.5.6 Exposure to Investigational Product

Replaced: investigational product with AMG 570.

Deleted: Details for each AMG 570 administration will be listed for each subject. In addition

10.5.7 Exposure to Concomitant Medication

Deleted: A subject listing of all concomitant medications will be provided.

10.6 Analysis of exploratory Efficacy Endpoints

Deleted: Listings by subject will be produced if deemed necessary for all endpoints listed below.

10.6.1 Disease Activity Score Based on 28 Joints (DAS 28-CRP)

Added: mg/L unit was added for CRP

10.7 Pharmacokinetic Analysis

Added: Pharmacokinetics analyses will be performed by Clinical Pharmacology, Modeling and Simulation (CPMS) group.

Deleted: by Clinical Pharmacology, Modeling and Simulation (CPMS) group.

10.7 Pharmacodynamic Analysis

Deleted: Following analytes were deleted from analysis since these analytes are of exploratory nature and may be collected and analyzed by separate department (eg, Computational Biology) in future.

- circulating Plasma cells by flow cytometry and gene signature
- circulating Tfh by gene signature

Added:

Added Percentage change from baseline for summary of PD data.

Added:

For selected analytes, plots of selected summary statistics (eg, mean, mean change, mean fold change or mean percent change) over time may be plotted by treatment group as deemed necessary.

Deleted:

Listings by subject will be produced if deemed necessary.