Statistical Analysis Plan

Protocol Title:	A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Rheumatoid Arthritis With Inadequate Response to Standard of Care Therapy
Short Protocol Title:	Safety and Efficacy of AMG 592 in Subjects with Active Rheumatoid Arthritis
Protocol Number:	20170149
NCT Number:	NCT03410056
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	12 December 2017	NA
[Amendment 1 (v2.0)]	**7 February 2020**	**Changes related to recent protocol amendment 3 (dated 6 June 2019)** **Removal of non-critical listings** **Clarifications added for analyses**

Note: Please see the Appendix F for detailed summary of changes and rationale for changes.

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[redacted]

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ALT	alanine transaminase
ANA	anti-nuclear antibody
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
AST	aspartate transaminase
ATG	antithymocyte globulin
CRF	case report form
CRP	C-reactive protein
CTCAE	common terminology criteria for adverse events
CPMS	clinical pharmacology, modeling and simulation
DAS-28-CRP	disease activity score (28 joints) calculated using the C-reactive protein formula
DAS-28-ESR	disease activity score (28 joints) calculated using the erythrocyte sedimentation rate formula
DLRM	dose level review meeting
DMP	data management plan
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
FACTS	Fixed and Adaptive Clinical Trial Simulator
[redacted]	
IPD	Important protocol deviation
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
LOCF	Last observation carried forward
MAD	multiple ascending dose
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Physical component summary
PD	pharmacodynamics
PK	pharmacokinetic
PGA	Physician global assessment of disease activity
POS	probability of success
QTc interval	QT interval corrected for heart rate using accepted methodology
[redacted]	
RA	rheumatoid arthritis

Abbreviation or Term	Definition/Explanation
RF	rheumatoid factor
RP2D	recommended phase 2 dose
[redacted]	
SAP	Statistical Analysis Plan
SC	subcutaneous
[redacted]	
SGA	Subject (patient) global assessment of disease activity
[redacted]	
TEAE	treatment emergent adverse event
[redacted]	
T_{max}	time of maximum observed concentration
TNF	tumor necrosis factor
Treg	T regulatory cells
WHODRUG	world health organization drug

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 study 20170149, AMG 592 dated **6 June 2019.** The scope of this plan includes the Dose Level Review Meetings (DLRM) in phase1b, the interim analysis in phase 2a and the primary analysis in phase1b and phase 2a that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1b • To evaluate the safety and tolerability of subcutaneous (SC) dose administrations of AMG 592 in subjects with active rheumatoid arthritis (RA)	**Phase 1b** • Treatment-emergent adverse events. • Clinically significant changes in vital signs, laboratory safety tests, and electrocardiograms (ECGs)
Phase 2a • To evaluate the efficacy of AMG 592 at week 12 as measured by the American College of Rheumatology 20% improvement criteria (ACR 20) in adult subjects with moderate to severe RA	**Phase 2a** • ACR 20 at week 12
Secondary	
Phase 1b • To characterize the pharmacokinetic (PK) profile following treatment with AMG 592	**Phase 1b** • AMG 592 serum concentration and 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_{tau}) after the first and last doses.
• To evaluate the incidence of anti-AMG 592 antibody formation and cross-reactivity to human IL-2.	• Anti-AMG 592 antibodies and cross-reactivity to IL-2. • Anti-AMG 592 and anti-IL-2 neutralizing antibodies

Objectives	Endpoints

• **Phase 2a**
  • To evaluate the effect of treatment with AMG 592 on other measures of disease activity at week 12
	• **Phase 2a**
	  • ACR 50/70 at week 12
	  • Disease activity score (28 joints) calculated using the erythrocyte sedimentation rate formula (DAS28-ESR) and change from baseline at week 12
	  • Disease activity score (28 joints) calculated using the C-reactive protein formula (DAS-28-CRP) and change from baseline at week 12

• To evaluate the safety of AMG 592	• Treatment-emergent adverse events. • Clinically significant changes in vital signs, laboratory safety tests
• To characterize the PK of AMG 592 in subjects with RA	• AMG 592 serum concentration and PK parameters
Exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

2.2 Hypotheses and/or Estimations

Phase 1b

AMG 592 is safe and well tolerated in subjects with active RA.

[redacted]

3. Study Overview

3.1 Study Design

Phase 1b

The phase 1b part of the study is a double-blind, placebo controlled, multiple ascending dose (MAD) study to evaluate the safety, tolerability, PK, and PD of AMG 592 in subjects with active RA with inadequate response to standard of care therapy (ie, methotrexate and other standard of care therapies as defined in the summary of eligibility criteria and Section 6.1 and 6.2 of the study protocol). Subjects will be treated for a total of 12 weeks after which they will be followed for an additional 6 weeks for safety and additional PK/PD data collection.

The phase 1b will include 4 **planned** dosing-cohorts. Subjects within a dosing-cohort will be randomized in a 3:1 ratio to AMG 592 (n = 6) or placebo (n = 2) as follows: cohort 1

[redacted]placebo [redacted] cohort 2 [redacted]); cohort 3 [redacted] and cohort 4 [redacted] in addition to standard of care therapy. **Approximately 8 additional subjects (6 AMG 592; 2 placebo) may be enrolled into each of cohorts 2 and 3.** Dosing cohorts will enroll sequentially with the exception of cohorts 2 and 3, which will enroll concurrently. A **Dose Level Review Meeting (**DLRM**)** will convene after the last subject in each cohort completes the week 4 visit. **For cohorts 2 and 3 an additional DLRM will convene after the first 16 enrolled subjects (8 in each cohort) complete the week 4 visit.** The decision to dose the next cohort will be based on the aggregated review of safety data. After incidents of interest (including selected adverse events or intolerable PD levels) are observed, a Bayesian logistic regression model (BLRM) (Bailey et al, 2009; Neuenschwander et al, 2008) will be implemented to model these events to aid dosing decisions for each DLRM. DLRM members will be 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. Additional dosing cohorts may be added **and/or existing cohorts may be expanded** based on emerging data. [redacted]

[redacted] The phase 2a part of the study will commence after a RP2D is identified in the phase 1b part of the study.

[redacted]

3.2 Sample Size

3.2.1 Phase 1b

It is anticipated that approximately **48** subjects will be **randomized** in the phase 1b part of the study with 8 subjects **randomized to each of cohorts 1 and 4 and approximately 16 subjects randomized to each of cohorts 2 and 3. The total sample size may be higher than 48 subjects if DLRM recommended additional dosing cohorts and/or expansion of existing cohorts, or replacement of subjects. Additional subjects may be enrolled in each cohort to enable all screened eligible subjects to participate in the study. Within each cohort subjects will be randomized to AMG 592 or placebo in a 3:1 ratio.**

The sample size of the phase 1b part of the study is based on practical considerations. With 6 subjects receiving AMG 592 per cohort, there is an 82% chance of at least 1 subject experiencing an adverse event, if the true event rate is 25%. The chance of at least 1 subject experiencing an adverse event will be 74% if the event rate becomes 20%. With a total of 24 subjects planned to receive AMG 592 in phase 1b, there is a 21% chance of at least 1 subject experiencing an adverse event with a true event rate of 1%. The chance of at least 1 subject experiencing an adverse event will be 71% if the true event rate becomes 5%.

In case of expansion of cohorts 2 and 3, with 12 subjects receiving AMG 592 in cohort 2 and 3, the chance of at least 1 subject experiencing an adverse event within that cohort increases to 97% and 93% for true events of 25% and 20% respectively. In addition, with a total of 36 subjects planned to receive AMG 592 in the phase 1b part of the study in case of expansion of cohorts 2 and 3, the chance of at least 1 subject experiencing an adverse event across the cohorts increases to 30% and 84% if the true event rates are 1% and 5% respectively.

[redacted]

4. Covariates and Subgroups

4.1 Planned Covariates

4.1.1 Phase 1b

There are no pre-specified covariates.

[redacted]

4.2 Subgroups

4.2.1 Phase 1b

There are no pre-specified subgroup analyses.

[redacted]

5. Definitions

5.1 Basic Definitions

Investigational Product

AMG 592 and placebo.

Actual Treatment

The actual treatment that the subject received during the study phase. If subject received at least one dose of AMG 592, then the subject's actual treatment group is AMG 592.

For interim analysis, if a subject who randomized to the AMG 592 group hasn't received any AMG 592 dose yet, the subject's actual treatment group is considered as AMG 592 for the interim analysis, to minimize potential inconsistency with the primary analysis.

[redacted]

[redacted]

5.2 Study Points of Reference

5.2.1 Phase 1b

Baseline

The last measurement for the endpoint of interest, which will be taken **prior to or on** the first dose of investigational product in phase 1b of this study**, unless stated otherwise**.

Study Day 1

The first day of investigational product administration in the phase 1b of this study.

Study Day

Study day is defined as the number of days from Day 1.

Before Study Day 1:

Study Day = (Date of Interest – Date of Study Day 1)

After Study Day 1:

Study Day = (Date of Interest – Date of Study Day 1) + 1

End of Study Date

The end of study date is recorded on the End of Study CRF.

Enrollment (Randomization) Date

The date on which a subject is assigned to receive AMG 592 or placebo through the IVRS. **The enrollment date will be collected in enrollment eCRF.**

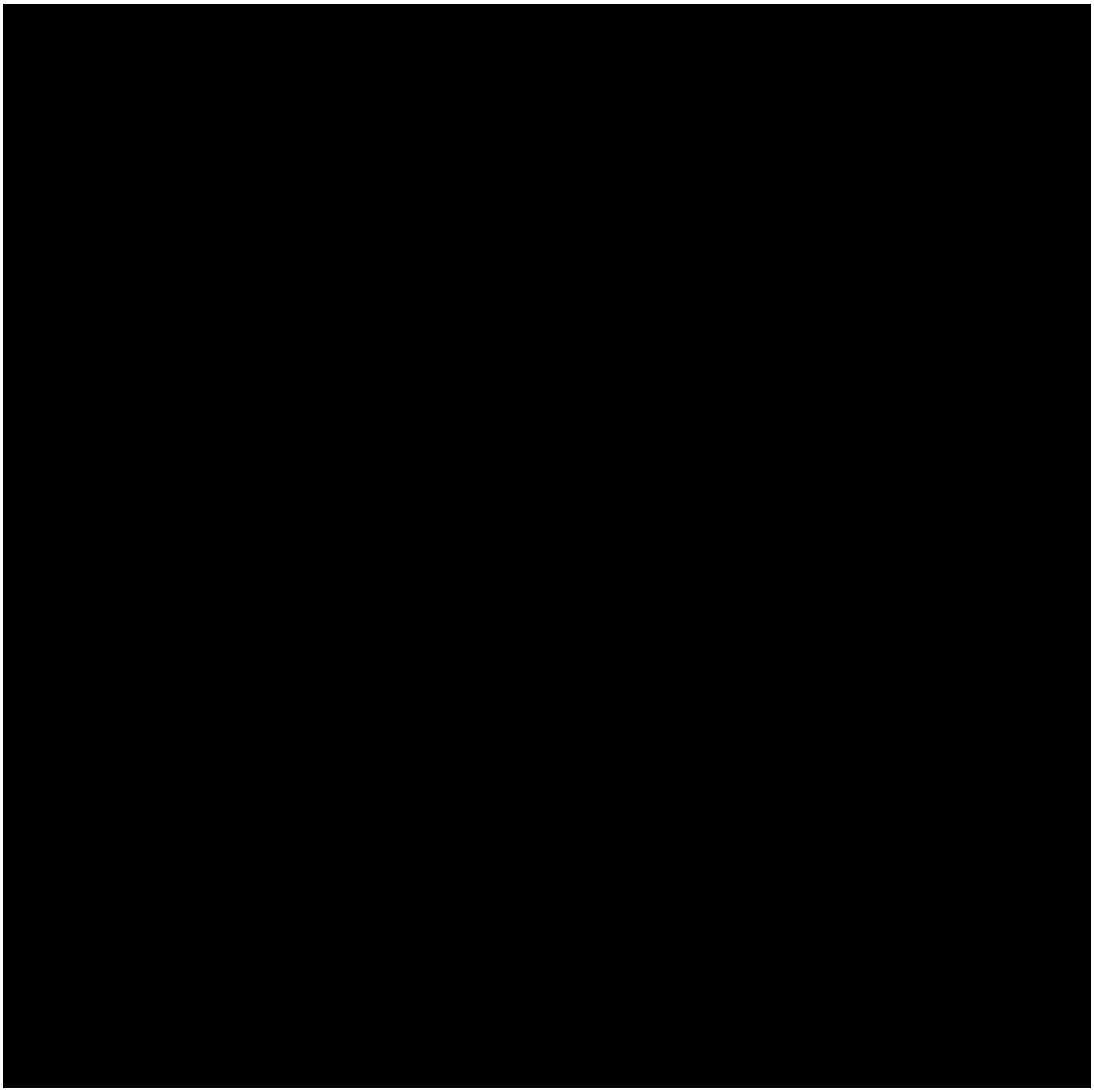
End of Investigational Product Date

The date on which a subject is administered the last dose of investigational product.

Study Visit

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the analysis visit **as per the analysis visit windows described in Appendix E.**

[redacted]



5.3 Definitions of Study Endpoints

- **ECG analysis value**
- **ECGs will be performed in triplicate, approximately 30 seconds apart, at time points specified in the Schedule of Assessments in the protocol. On day -1 baseline, 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 minutes after the last assessment of a triplicate at a time point will be included in the mean for that time point.

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

Change from Baseline

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

Percent Change from Baseline

Percent change from Baseline is the arithmetic difference between post-Baseline and Baseline divided by Baseline values times 100. If the change from baseline is not equal to 0 and the baseline value is 0 then percent change is not defined. If the change from baseline is equal to 0 and the baseline value is also 0 then percent change is 0.

Fold change from Baseline

Fold change from Baseline equals the post-Baseline value divided by the Baseline value. If the change from baseline is not equal to 0 and the baseline value is 0 then fold change is not defined. If the change from baseline is equal to 0 and the baseline value is also 0 then fold change is 1.

Improvement from Baseline

For endpoints where, higher score indicates better clinical outcome, improvement is defined as post-baseline value -baseline value. For endpoints where, lower score indicates better clinical outcome, improvement is defined as baseline value- post-baseline value.

[redacted]

[redacted]

ACR 20

A positive ACR 20 response is defined as at least 20% improvement from baseline in both TJC and SJC, and a 20% improvement or more in at least 3 of the following 5 criteria: physician global assessment of disease activity (PGA, 0-100 scale), subject (patient) global assessment of disease activity (SGA, 0-100 scale), patient global assessment of joint pain (0-100 visual analog scale), subject self-assessment of disability (Health Assessment Questionnaire, HAQ-DI), and acute phase reactant: C-Reactive Protein (CRP).

[redacted]

ACR 50

A positive ACR 50 response is defined by using the definition of ACR 20 response described above but requiring at least 50% improvement.

ACR 70

A positive ACR 70 response is defined by using the definition of ACR 20 response described above but requiring at least 70% improvement.

DAS28-CRP

The DAS28-CRP is a composite score that is based on a 28-joint count (using TJC28 and SJC28), CRP (in mg/L), and SGA. [redacted]

DAS28-ESR

The DAS28-ESR is a composite score that is based on a 28-joint count (using TJC28 and SJC28), ESR (in mm/hour), and SGA. [redacted]

[redacted]

Incidents of Interest

Incidents of interest such as selected adverse events or intolerable PD levels will be identified after safety data is collected and before each DLRM convenes. Number of incidents of interest according to treatment received will be used in the BLRM for the DLRM analysis to aid decision in DLRMs. The incidents of interest will be listed in the separate document of analysis plan for DLRM. The list can be updated to include emerging incidents as data get collected.

Adverse Event

This includes all adverse events /serious adverse events and disease-related events as identified on the Adverse Events eCRF.

Treatment Emergent Adverse Event (TEAE)

A treatment emergent adverse event is any adverse event (including disease-related events) 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 or not on the Adverse Events eCRF) and up to and including 42 days after the end of investigational product or the End of Study date, whichever is earlier.

Disease Related Event

Events anticipated to occur in the study population due to the underlying disease. Protocol lists joint pain, joint stiffness, joint swelling, and worsening of

rheumatoid arthritis as disease related events. These will be identified on the Adverse Events eCRF.

QTcB

QTcB by Bazett's formula will be derived as:

$QTcB\ (msec) = QT(msec)/\sqrt{(60/HR(cycle/min))}$

QTcF

QTcF by Fridericia's formula will be derived as:

$QTcF\ (msec) = QT(msec)/\sqrt[3]{(60/HR(cycle/min))}$

5.4 Demographic and Characteristics

Age

Age in years at randomization, which is collected **in** the eCRF.

RA disease duration

Number of years from the date of diagnosis of RA **(collected in medical history eCRF)** to the date of Study Day 1 in the current study period.

Time on methotrexate

Number of weeks from the date of initial prescription of methotrexate to the date of Study Day 1 in the current study period.

Methotrexate dose

Average weekly total methotrexate dose in mg during the screening period.

Prior and Concomitant medications

Prior medication is defined as any medication that with start date prior to the first dose date of study drug. Concomitant medication is defined as any medication with start date prior to the first dose date of study drug but which continued to be taken after the first dose of study drug or any medication with start date on or after the first dose date and up to and including 42 days after the last dose date.

6. Analysis Sets

6.1 Phase 1b

Subjects will be analyzed according to the actual treatment received.

6.1.1 Safety Analysis Set

The safety analysis set for phase 1b consists of all subjects who received at least 1 dose of investigational product. The safety analysis set will be used for the phase 1b analyses unless otherwise specified.

6.1.2 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

6.1.2.1 Pharmacokinetic Concentration Analysis Set

The PK concentration analysis set for phase 1b consists of all subjects who have received at least one dose of AMG 592 and have at least one quantifiable PK sample collected.

6.1.2.2 Pharmacokinetic Parameter Analysis Set

The PK parameter analysis set for phase 1b consists of all subjects who have received at least one dose of AMG 592 and for whom at least one PK parameter is adequately estimated.

[redacted]

[redacted]

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Phase 1b

There is no formal interim analysis for phase 1b.

DLRM analyses will be conducted after the last subject in each cohort completes the week 4 visit, with an exception for cohorts 2 and 3 where the analysis will be conducted after the last subject enrolled in both cohorts completes the week 4 visit.

The study statistician will perform the analyses and provide the result to the DLRM before the meeting convenes. The DLRM members will conduct aggregated review of safety data and the analyses results to make dosing decisions.

The scope of the DLRM analyses includes a Bayesian logistic regression model (BLRM) [redacted], where posterior probabilities of incident of interest at each dose level will be summarized and reported. In addition, safety data including demographics, medical history, concomitant therapies, adverse events, electrocardiograms, vital signs, laboratory results, and emerging pharmacokinetic and pharmacodynamics data will be listed or plotted. For a complete list of planned outputs including subject level listings and line plots refer to a separate SAP for DLRM.

[redacted]

7.2 Primary Analysis

7.2.1 Phase 1b

The primary analysis will be done after all subjects have had the opportunity to complete the study and performed the safety follow-up.

[redacted]

8. Data Screening and Acceptance

8.1 General Principles

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

8.2 Data Handling and Electronic Transfer of Data

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

8.3 Handling of Missing and Incomplete Data

If there are missing or incomplete start and/or stop dates for **adverse events, prior and** concomitant medication**s, or medical history events and the analysis requires complete dates, then dates are imputed as per** the imputation rules provided in Appendix A. **No imputation is performed if there is no need of these dates for the analysis.**

Laboratory measurements that are below the lower quantification limits will be considered equal to the lower limit of quantification for all analyses unless explicitly noted otherwise.

[redacted]

Subject may have missing study endpoint data for a variety of causes. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular timepoint. The general procedures outlined below describe what will be done when endpoint data is missing.

8.3.1 Phase 1b

All endpoints in the phase 1b part of the study will be analyzed as-is and no imputation is planned [redacted]

[redacted]

[redacted]

8.4 Detection of Bias

Important protocol deviations and early withdrawal from treatment and from study may bias the results of the study. The incidence of these factors will be assessed and reason for early withdrawals will be tabulated.

8.5 Outliers

Outlier data will not be excluded unless scientifically justified.

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

8.6 Distributional Characteristics

Not Applicable

8.7 Validation of Statistical Analyses

Programs will be developed, 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.

9. Statistical Methods of Analysis

9.1 General Considerations

Analyses of phase 1b data will be provided separately than analyses of phase 2 data. Descriptive statistics will be provided for selected demographics, safety, 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 presented and summarized by treatment and by time as appropriate. **Data collected at unscheduled visits or timepoints will be included in the analysis unless stated otherwise.**

Only critical subject-level data listings will be provided in the Clinical Study Report. Additional listings of subject-level data will be reviewed as part of DLRMs or ongoing data review for assessment of product's safety, efficacy and the quality of data, but will not be included in the Clinical Study Report.

9.2 Subject Accountability

Phase 1b [redacted]

The number and percent of subjects who were enrolled, received at least one dose of 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 overall and 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 summary of number of subjects in each analysis subset will be provided.

9.3 Important Protocol Deviations

Phase 1b [redacted]

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study.

The final IPD list is used to produce the list of subjects with IPDs.

Eligibility deviations are defined in the protocol. A list of deviations from eligibility criteria will also be generated.

9.4 Demographic and Baseline Characteristics

The full analysis set will be used to summarize subject demographics and baseline disease characteristics.

Phase 1b [redacted]

9.4.1 Demographic

- Age (years) at enrollment (continuous summary statistics)
- **Age categories (number and percent of subjects in 18 – 64 and 65 - 70 years)**
- Sex (number and percentage of males and females)
- Ethnicity (number and percentage of Hispanic or Latino and Not Hispanic or Latino)
- Race (number and percentage of subjects in each race, or mixed-race combination)

9.4.2 Baseline Characteristics

- Height and weight (continuous summary statistics)
- Duration of RA **(years) (continuous summary statistics)**
- **Prior** medication uses **for RA indication (number and percentage of subjects)**
- **Time on Methotrexate (weeks) (continuous summary statistics)**
- **Average weekly Methotrexate dose (mg) (continuous summary statistics)**
- **Rheumatoid factor (continuous summary statistics)**
- **Anti-cyclic citrullinated peptide (anti-CCP) antibody value (continuous summary statistics)**

9.5 Efficacy Analyses

Table 9-1. Efficacy Endpoint and Analysis Method Table Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Primary Endpoint		
Phase 1b: The primary endpoint of phase 1 is not an efficacy endpoint. [redacted] ACR 20 at week 12	[redacted]	
Secondary Endpoints		
[redacted] ACR 50/70 at week 12	[redacted]	
[redacted] DAS28-ESR/CRP		

The full analysis set will be used for primary analyses of the primary and secondary efficacy endpoints unless otherwise specified. The analysis set to be used for sensitivity analysis will be specified in this section.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

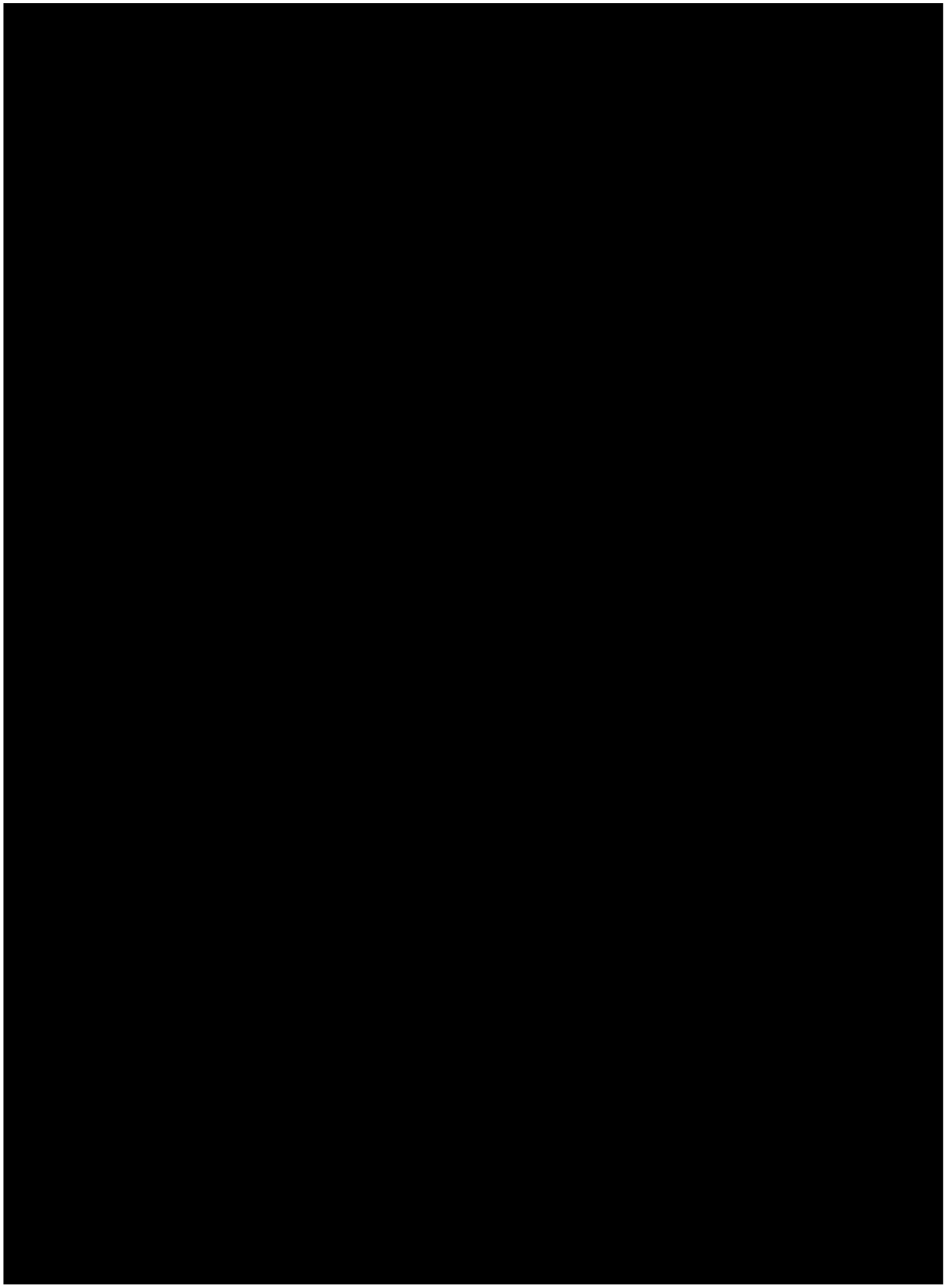
The primary endpoint for phase 1b is not an efficacy endpoint. The primary endpoint for [redacted] is ACR 20 at week 12.

[redacted]

[redacted]

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Phase1b does not include any secondary efficacy endpoints.



[redacted]

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Phase 1b

The primary endpoint for phase 1b is safety. The analysis will include the descriptive summary statistics for adverse events, disease-related events, laboratory measures, vital signs, physical measurements and ECG. Details are described in respective section below.

[redacted]

9.6.2 Adverse Events

Phase 1b [redacted]

The Medical Dictionary for Regulatory Activities (MedDRA) version 20 or later will be used to code all adverse events to a system organ class and a preferred term. The severity of each adverse event will be graded using CTCAE criteria version 4.0 **or later (see Appendix C)**.

An overall summary of treatment-emergent adverse events by toxicity grade and type will be provided.

Subject incidence of all treatment-emergent, serious treatment emergent, treatment-related, **serious treatment-related,** adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class in alphabetical order and preferred term in descending order of frequency. **Treatment emergent adverse events and treatment-related adverse events will also be tabulated by preferred term and worst severity grade.**

Subject incidence of disease-related events will also be summarized **separately** for all treatment-emergent disease-related events and fatal disease-related events.

[redacted]

9.6.3 Laboratory Test Results

Phase 1b [redacted]

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

Summaries of chemistry and hematology laboratory data will include baseline value, values and change from baseline at scheduled visits.

Shift tables indicating the change between the baseline and the maximum post dose CTCAE grades **based on CTCAE version 4.0 or later** will be provided for selected laboratory parameters of interest.

A listing of normal ranges of lab analytes will be included. Further, a listing of CTCAE grade 3 or higher laboratory toxicities will be provided **for subjects with grade 3 or higher toxicity for any of the parameters included in the shift table**. This listing will include **all available** data **for** laboratory parameter**s included in shift table** in order to provide proper context. **Values outside the normal laboratory reference ranges will be flagged as high or low and corresponding CTCAE grades will be included in the listing.**

9.6.4 Vital Signs

Phase 1b [redacted]

The analyses of vital signs will include summary statistics at selected time points**, post-baseline maximum/minimum and change from baseline to post-baseline maximum/minimum** by treatment group for systolic/diastolic blood pressure, heart rate and temperature.

9.6.5 Physical Measurements

Phase 1b

The analyses of physical measurements will include summary statistics **of weight** at **scheduled** time points by treatment group.

9.6.6 Electrocardiogram

Phase 1b

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters (PR, QRS, QTcF, QTcB, RR). Subjects' maximum change from baseline in QTcF, **and** QTcB 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.

[redacted]

9.6.7 Antibody Formation

Phase 1b [redacted]

The incidence and percentage of subjects who develop anti-AMG 592 antibodies (binding and if positive, neutralizing) at any time will be tabulated by **treatment group**.
The incidence and percentage of subjects who develop anti-AMG 592 antibodies that cross-react to IL-2 and who develop anti-IL2 neutralizing antibodies will also be tabulated

9.6.8 Exposure to Investigational Product

Phase 1b [redacted]

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group.
The number of days on investigational product, **and** the cumulative total dose of investigational product will be summarized **for each treatment group**. Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.
A listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

9.6.9 Exposure to Concomitant Medication

Phase 1b [redacted]

Number and proportion of subjects receiving concomitant medication for RA indication will be summarized by preferred term or category as coded by the World Health Organization Drug (WHODRUG) dictionary by treatment group.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

9.7.1.1 Analysis of Pharmacokinetic Endpoint

Phase 1b [redacted]

The Pharmacokinetic Concentration Analysis set defined in Section 6 will be used in analyzing PK concentration data and the Pharmacokinetic Parameter Analysis Set will be used in analyzing PK parameters. Plasma concentrations of AMG 592 will be expressed in ng/mL. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the lower limit of quantification will be treated as zero in summary statistics.

Nominal sampling times will be used for individual concentration-time plots and tables. Actual dose administered, and actual sampling times will be used for the calculation of PK parameters for each subject. The reasons for excluding any sample from the analyses will be provided.

Individual concentration-time data will be tabulated and presented graphically. Summary of PK concentration over time and PK parameters will be provided. Mean concentration-time profiles for each dose will be provided.PK parameters will be summarized for each dose using descriptive statistics, including, but not limited to mean, standard deviation, CV, median and range. Analyses will be conducted by Amgen Clinical Pharmacology Modeling and Simulation (CPMS).

[redacted]

9.7.3 Analyses of Health Economic Endpoints

Not applicable for the study

[redacted]

10. Changes from Protocol-specified Analyses

ECG listing as planned in the protocol will not be provided because only critical data listings will be included in the CSR and summary tables planned for ECG data will be adequate to identify significant changes (if any) in ECG data.

11. Literature Citations / References

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12. Prioritization of Analyses

There is no prioritization of analyses.

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 and do not impute.

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

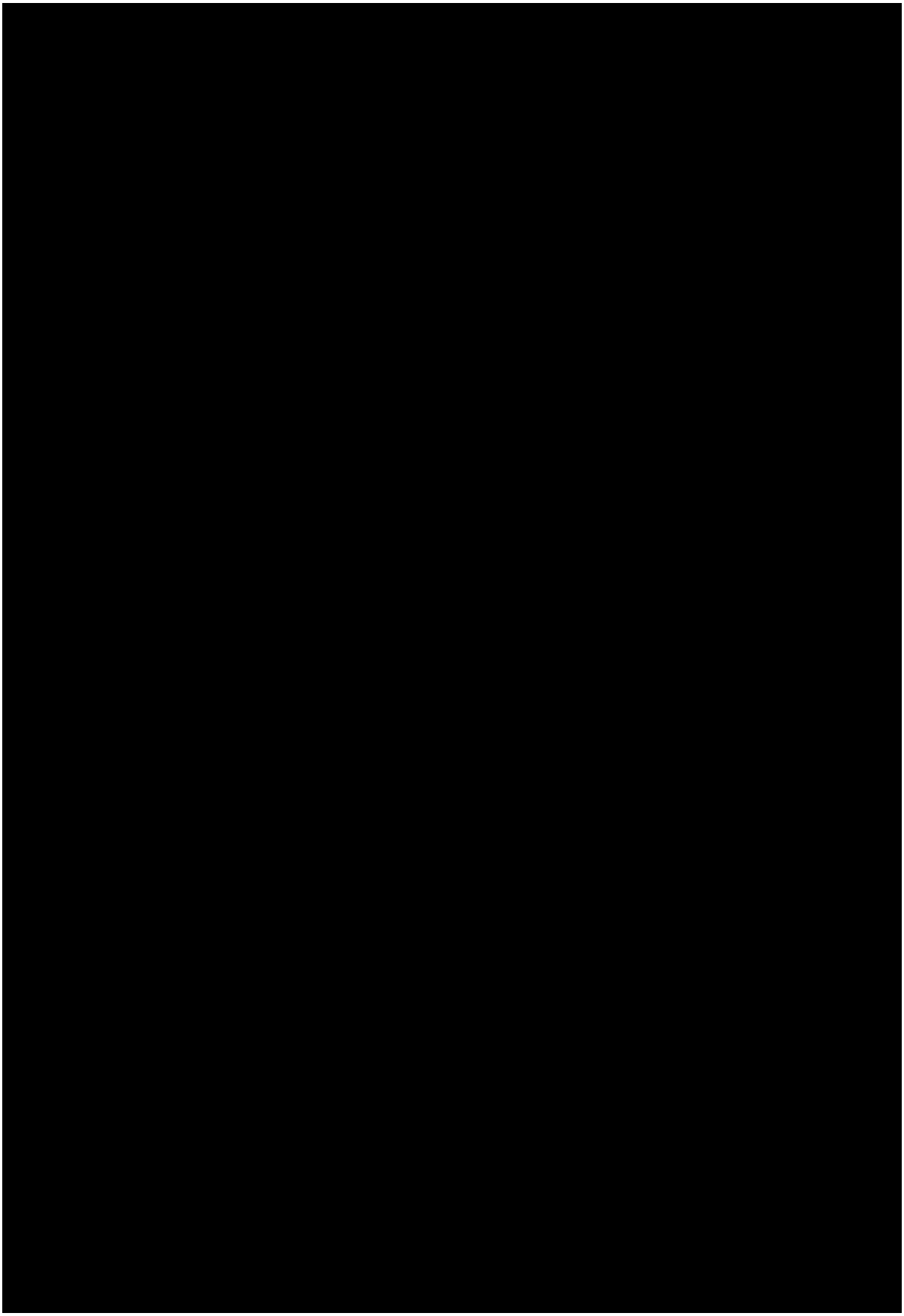
1 = Impute the date of first dose

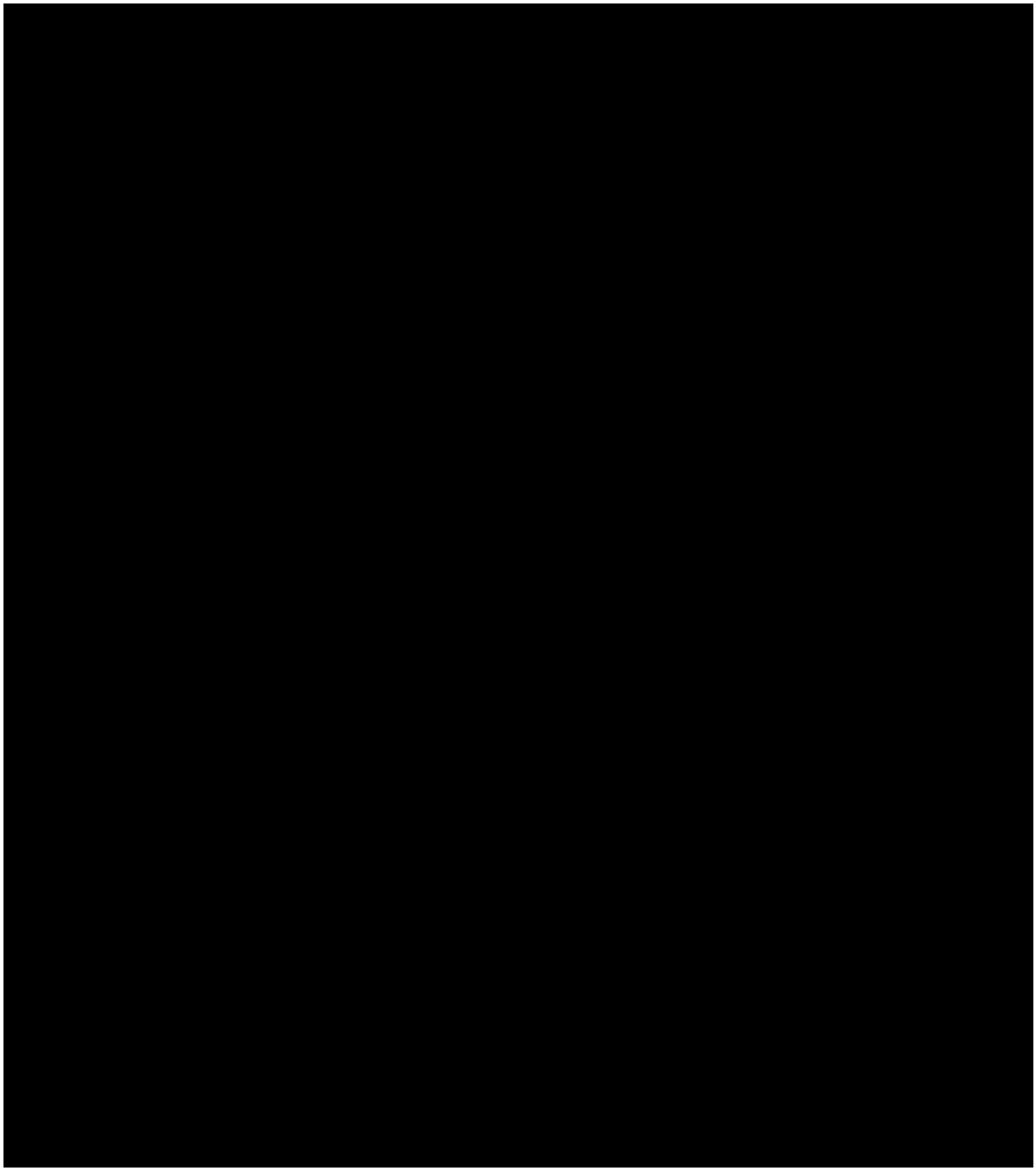
2 = Impute the first day of the month

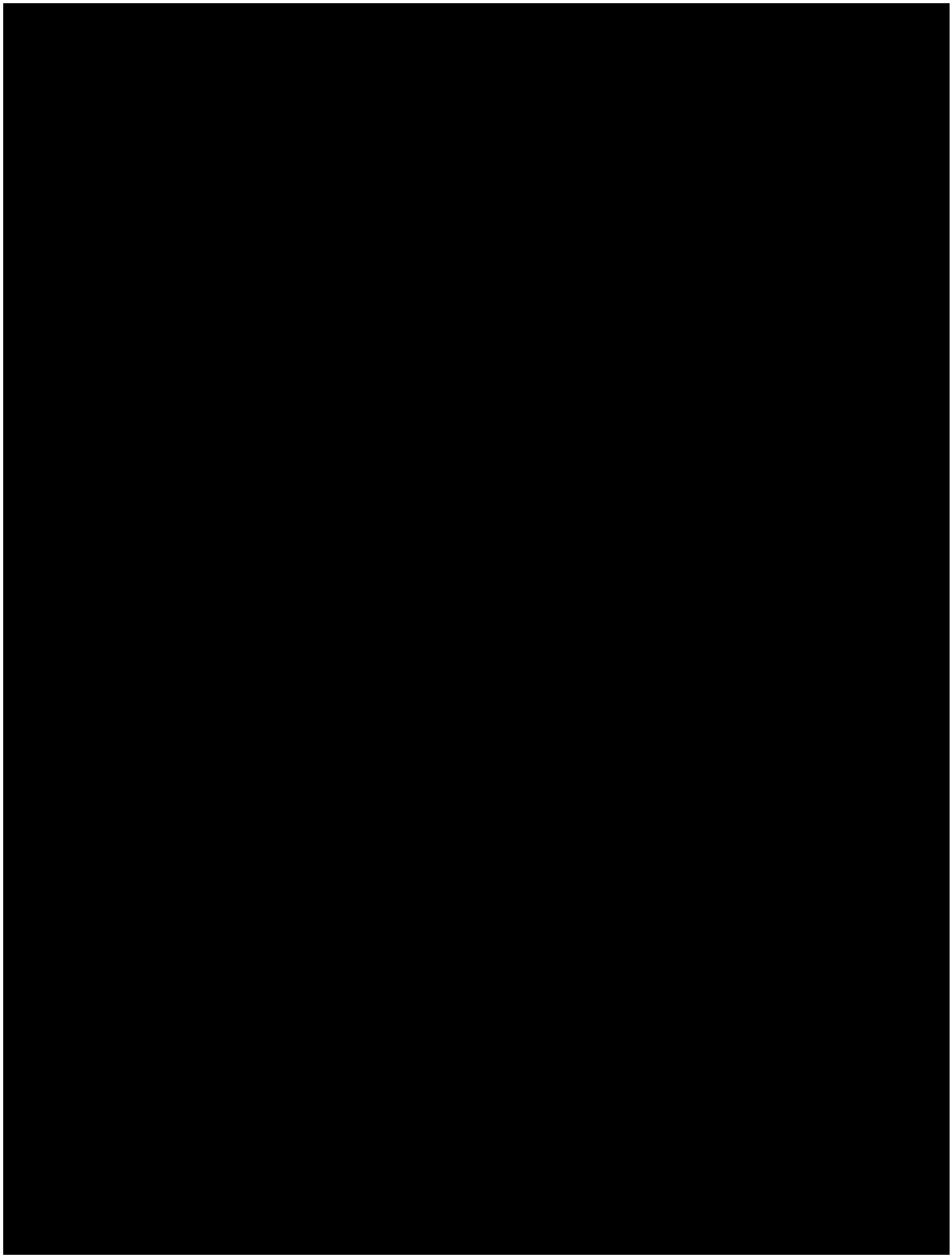
3 = Impute January 1 of the year

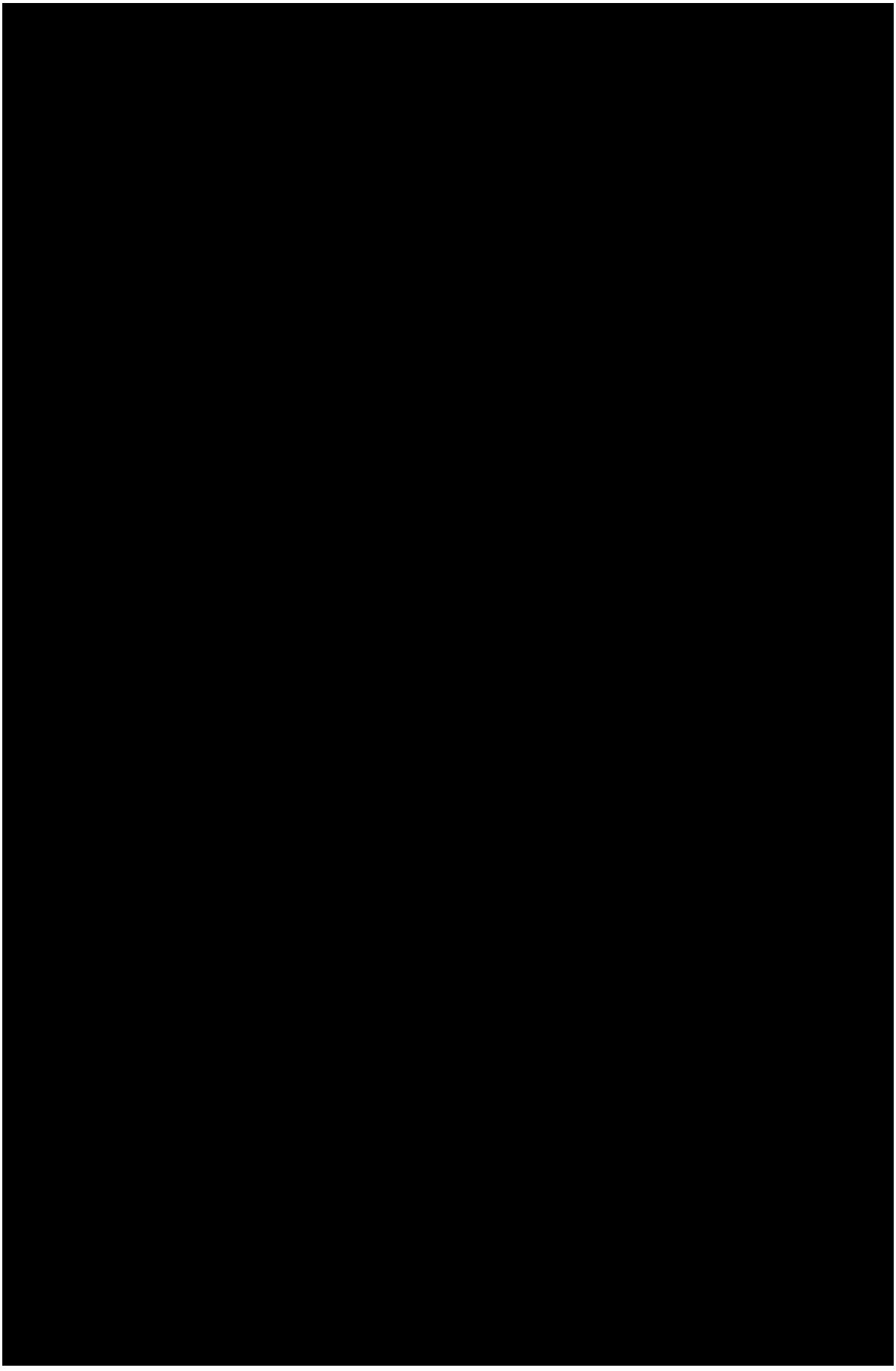
4 = Impute January 1 of the stop year

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





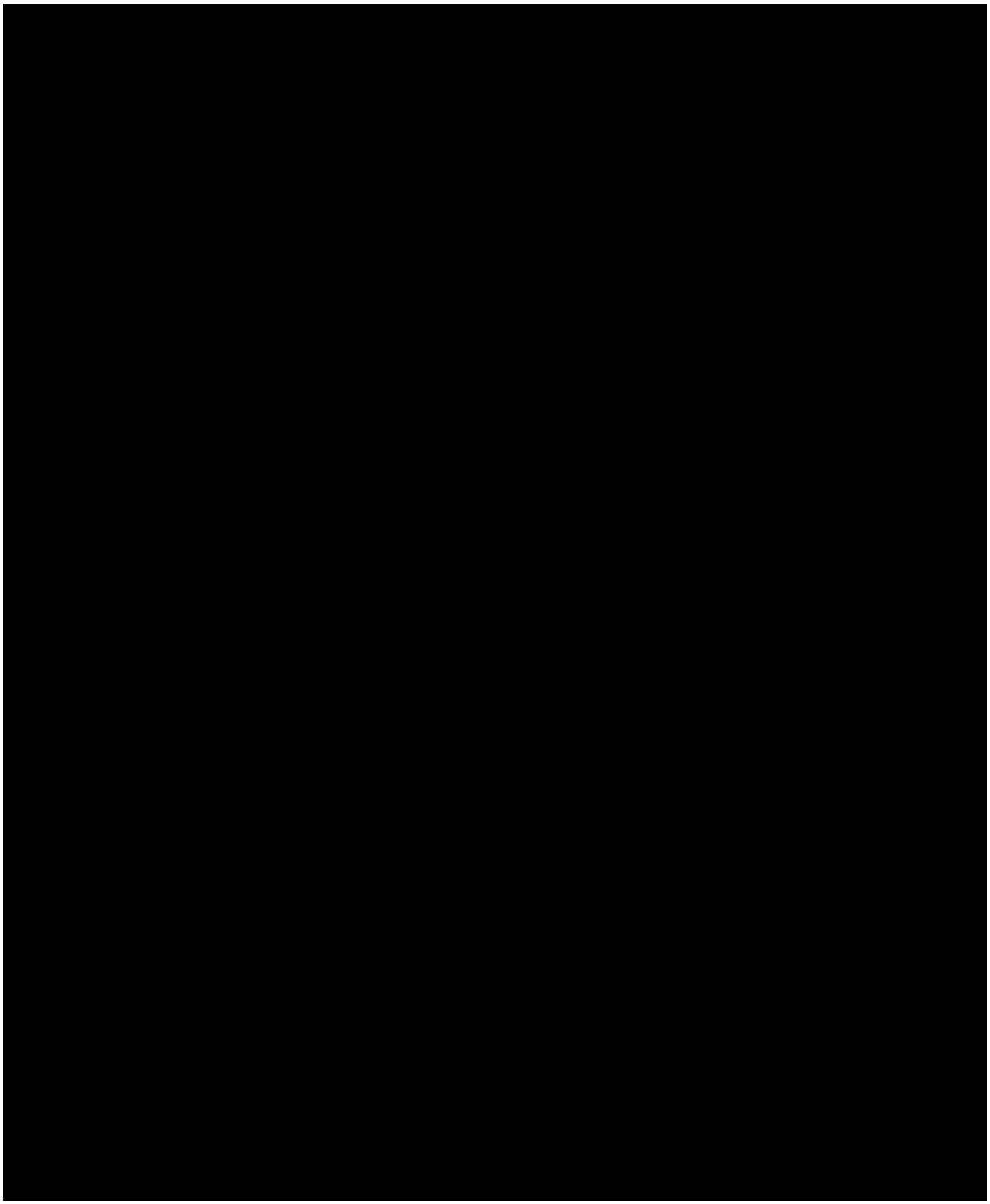




Appendix C. Reference Values/Toxicity Grades

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



Appendix E. Analytical Windows

The last visit with non-missing assessment prior to first dose will be defined as a baseline visit and the analysis visit name will be "Baseline". For any visit up to Day 1 pre-dose which is not a baseline visit, the analysis visit will be 'Pre-Analysis'. For post-dose assessments on Day 1 and assessments at Safety follow-up/EOS visit, the analysis visit will be same as the scheduled visit. Only for phase 1b, for post-dose assessments on Day 85 (the day corresponding to week 12 dosing), the analysis visit will be same as the scheduled visit. Remaining visits (scheduled or unscheduled) after Day 1 for any assessment will be mapped to the analysis visit based on visit windows defined in the tables below for that assessment. Only visits applicable for that assessment and phase of the study will be considered for analysis.

Data collected through central lab and local lab will both be mapped into analysis visit windows. The local lab data can only be used in analysis when there is no central lab data available in the analysis visit window.

If more than one visit with non-missing data falls within an analysis visit window, the visit closest to the target day will be considered for analysis. If two visits are equidistant from the target day, the latest visit (or time if on the same day) will be considered. If more than one evaluation has same date and time (for chemistry, hematology or pharmacodynamic results), the value with the smallest accession number will be considered.

Analysis visit windows for selected assessments are included in tables below. For remaining assessments, no visit window will be applied. Day 85 used in Study day window calculation in the tables below is the study day when Week 12 dose was received. If that dose is missing, then 85 is used for calculation.

Phase 1b

Vitals

Analysis Visit	Target Day	Study Day Window
Week 1, Day 2	2	2
Week 1, Day 3	3	3
Week 1, Day 4	4	4-6
Week 1, Day 8	8	7-9
Week 1, Day 11	11	10-12

Analysis Visit	Target Day	Study Day Window
Week n, Day 7*n+1 (n = 2, 3, 4, 5, 6, 7,8, 9, 10)	7n+1	Target day -2, Target day +4
Week 11, Day 78	78	76- (Day 85-3)
Week 12, Day 85 Pre-dose	85	Day 85-2, Day 85
Week 12, Day 86	86	Day 85 +1
Week 12, Day 87	87	Day 85 +2
Week 12, Day 88	88	Day 85 + 3
Week 13, Day 92	92	(Day 85 + 4) -96
Week 14, Day 99	99	97-106
Week 16, Day 113	113	>106

Chemistry, hematology, weight, and ECG (Phase 1b only)

Analysis Visit	Target Day	Study Day Window
Week 1, Day 2	2	2-3
Week 1, Day 8	8	4-12
Week 2, Day 15	15	13-22
Week n, Day 7*n+1 (n = 4, 6, 8)	7*n+1	Target day -6, Target day +7
Week 10, Day 71	71	65- (Day 85-7)
Week 12, Day 85	85	Day 85-6, Day 85 +7
Week 14, Day 99	99	(Day 85+8)-106
Week 16, Day 113	113	> 106

[redacted]

Antibody assessments, [redacted]

Analysis Visit	Target Day	Study Day Window
Week 2, Day 15	15	2-22
Week 4, Day 29	29	23-43
Week 8, Day 57	57	44- (Day 85 -14)
Week 12, Day 85	85	Day 85- 13, Day 85 +7
Week 14, Day 99	99	> Day 85 + 7

[redacted]

Appendix F. Summary of changes and rationale for changes to the SAP Amendment 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 7 February 2019.
- Header version number was replaced with Version 2.0.
- Removal of unnecessary listings as per recent process

1. INTRODUCTION

- **Replaced:** protocol date of 26 June 2017 **with** date 06 June 2019.

3. Study Overview

Updates to sections below reflect changes in the protocol

- 3.1 Study Design

Phase 1b:

Added:

Cohort 3 dose changed to [redacted]

Approximately 8 additional subjects (6 AMG 592; 2 placebo) may be enrolled into each of cohorts 2 and 3.

For cohorts 2 and 3 an additional DLRM will convene after the first 16 enrolled subjects (8 in each cohort) complete the week 4 visit.

- 3.2 Sample Size

Phase 1b

Sample size was increased from 32 to 48 subjects. 16 subjects were added to Cohorts 2 and 3.

Added:

Approximately 48 subjects will be randomized. 8 subjects randomized to each of cohorts 1 and 4 and approximately 16 subjects randomized to each of cohorts 2 and 3. The total sample size may be higher than 48 subjects if, DLRM recommended additional dosing cohorts and/or expansion of existing cohorts or replacement of subject. Additional subjects may be enrolled in each cohort to enable all screened eligible subjects to

participate in the study. Within each cohort subjects will be randomized to AMG 592 or placebo in a 3:1 ratio.

In case of expansion of cohorts 2 and 3, with 12 subjects receiving AMG 592 in cohort 2 and 3, the chance of at least 1 subject experiencing an adverse event within that cohort increases to 97% and 93% for true event rates of 25% and 20%, respectively. In addition, with a total of 36 subjects planned to receive AMG 592 in the phase 1b part of the study in case of expansion of cohorts 2 and 3, the chance of at least 1 subject experiencing an adverse event across the cohorts increases to 30% and 84% if the true event rates are 1% and 5%, respectively.

5. Definitions

Updates to sections below include additions of new definitions or updates to existing definitions to bring more clarity to the analysis.

- 5.1 Basic Definitions

[redacted]

[redacted]

[redacted]

5.2 Study Points of Reference

5.2.1 Phase 1b

Replaced:

Baseline

The last measurement for the endpoint of interest taken before the first dose of investigational product in phase 1b of this study.

With:

Baseline

The last measurement for the endpoint of interest taken prior to or on the first dose of investigational product in phase 1b of this study**,** unless stated otherwise.

Deleted: Study Visit Table corresponding to analysis visit windows. Instead added revised tables for analytical windows in Appendix E.

[redacted]

5.3 Definitions of Study Endpoints

Added: Definitions for ECG Analysis Value, Baseline ECG, Changes from Baseline, Percent Change from Baseline, Fold Change from Baseline, Improvements from Baseline, Percent Improvement from Baseline, [redacted] Adverse Events, Treatment Emergent Adverse Event, Disease Related Adverse Events, Prior and Concomitant medications were added.

ECG analysis value

ECGs will be performed in triplicate, approximately 30 seconds apart, at time points specified in the Schedule of Assessments in the protocol. On day -1 baseline, three sets of triplicate ECGs will be collected, with each set being ≥ 30 minutes apart (i.e. 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 minutes after the last assessment of a triplicate at a time point will be included in the mean for that time point

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.

Changes from Baseline

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

Percent Change from Baseline

Percent change from Baseline is the arithmetic difference between post-Baseline and Baseline and Baseline divided by Baseline values times 100. If the change from baseline is not equal to 0 and the baseline value is 0 then percent change is not defined. If the change from baseline is equal to 0 and the baseline value is also 0 then percent change is 0.

Fold change from Baseline

Fold change from Baseline equals the post- Baseline value divided by the Baseline value. If the change from Baseline is not equal to 0- and the baseline value is 0 then fold change is not defined. If the change from baseline is equal to 0 and the baseline value is also 0 then fold change is 1.

Improvement from Baseline

For endpoints where, higher score indicates better clinical outcome, improvement is defined as post-baseline value-baseline. For endpoints where, lower score indicates better clinical outcome, improvement is defined as baseline value post-baseline value.

[redacted]

[redacted]

Adverse Event

This includes all adverse events/serious adverse events and disease-related events as identified on the Adverse Events eCRF.

Treatment Emergent Adverse Events (TEAE)

Revised the definition to match with Amgen standard definition of TEAE

Replaced:

Adverse events that occurred after first dose of investigational product in the current study period

With:

A treatment emergent adverse event is any adverse event (including disease-related events) 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 or not on the Adverse Events eCRF) and up to and including 42 days after the end of investigational product or the End of study date, whichever is earlier.

Disease Related Event

Events anticipated to occur in the study population due to the underlying disease. Protocol lists joint pain, joint stiffness, joint swelling, and worsening of rheumatoid arthritis as disease related events. These will be identified on the Adverse Event eCRF.

Prior and Concomitant medications

Prior medication is defined as any medication that with start date prior to the first dose date of study drug. Concomitant medication is defined as any medication with start date prior to the first dose date of study drug but which continued to be taken after the first

dose of study drug or any medication that with start date on or after the first dose date and up to and including 42 days after the last dose date.

6. Analysis Sets

6.1 Phase 1b

Added:

Subjects will be analyzed according to the actual treatment received.

[redacted]

8.3 Handling of Missing and Incomplete Data

Added: Added imputation of missing start/stop dates in Appendix A. Added imputation for lab or biomarker data as below.

Laboratory measurements that are below the lower quantification limits will be considered equal to the lower limit of quantification for all analyses unless explicitly noted otherwise.

[redacted]

8.3.1 Phase 1b

Added: text in italics below

All endpoints in the phase 1b part of the study will be analyzed as-is and no imputation is planned [redacted]

[redacted]

9. Statistical Methods of Analysis

9.1 General Considerations

Added:

Analyses of phase 1b data will be provided separately than analyses of phase 2 data. Data collected at unscheduled visits or timepoints will be included in the analysis unless stated otherwise.

Only critical subject-level data listings will be provided in the Clinical Study Report. Additional listings of subject-level data will be reviewed as part of DLRMs or ongoing data review for assessment of product's safety, efficacy and the quality of data, but will not be included in the clinical study report.

9.4 Demographic and Baseline Characteristics

9.4.1 Demographic

Added: Age Category

Age categories (number and percent of subjects in 18 – 64 and 65 - 70 years)

9.4.2 Baseline Characteristics

Added: Time on Methotrexate (weeks), average weekly Methotrexate dose (mg), rheumatoid factor, and anti-cyclic citrullinated peptide (anti-CCP) antibody value.

[redacted]

9.6.2 Adverse Events

Added:

Treatment emergent adverse events and treatment-related adverse events will also be tabulated by preferred term and worst severity grade.

9.6.4 Vital Signs

Added: below text in italics

The analyses of vital signs will include summary statistics at selected time points, *post-baseline maximum/minimum and change from baseline to post-baseline maximum/minimum* by treatment group for systolic/diastolic blood pressure, heart rate and temperature.

[redacted]

[redacted]

10 Changes from Protocol specified analyses

Added:

ECG listing as planned in the protocol will not be provided because only critical data listings will be included in the CSR and summary tables planned for ECG data will be adequate to identify significant changes (if any) in ECG data.

14. Appendices

Appendix A.

Added: Table for Imputation Rules for Partial or Missing Stop Dates

Appendix E.

Added: Tables for analytical windows for phase1b [redacted]