TITLE PAGE

Statistical Analysis Plan

A Phase 1, Open-label, Sequential-group, Single-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AMG 592 Administered Subcutaneously in Healthy Chinese, Japanese, and Caucasian Subjects

SAP Status: Final
SAP Version: 3.0
SAP Date: 20May2022

Investigational Medicinal Product: AMG 592 (efavaleukin alfa)

Protocol Reference: 20200102
Covance Study: 8448873

Sponsor:
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320 USA

Study Site:
Covance Leeds Clinical Research Unit
Springfield House, Hyde Street,
Leeds, LS2 9LH,
UK

Principal Investigators:

PPD

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LIST OF IN-TEXT TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

ADaM	Analysis Data Model
AE	adverse event
ANOVA	analysis of variance
AUC	area under the serum concentration-time curve
AUC_{inf}	area under the serum concentration-time curve from time zero to infinity
AUC_{last}	AUC from time zero to the last quantifiable concentration
BLQ	below the limit of quantification
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent total serum clearance
C_{max}	maximum observed serum concentration
COVID-19	coronavirus disease 2019
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
Foxp3	forkhead box P3
GLSM	geometric least squares mean
ICF	informed Consent Form
ICH	International Council for/Conference on Harmonisation
LLOQ	lower limit of quantification
ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{inf}	mean residence time observed from time zero to infinity
NK	natural killer
PD	pharmacodynamic(s)
PE	physical examination
PK	pharmacokinetic(s)

SAP	statistical analysis plan
SC	subcutaneous
SEM	standard error of the mean
SD	standard deviation
SDV	source document verification
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time of the maximum observed concentration
Tcon	Conventional T Cells
Treg	Regulatory T Cells
V_z/F	apparent volume of distribution during the terminal phase
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

This SAP is to provide details of statistical analysis that have been outlined within the clinical study protocol for study 20200102 (Final Version dated 01 April 2021, Amendment 1 dated 08 December 2021, Amendment 2 dated 28 April 2022) and electronic case report form (eCRF).

This SAP describes the planned analysis of the pharmacokinetic (PK), pharmacodynamic (PD), safety, and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Amgen Inc. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation.

This SAP must be finalized prior to the lock of the clinical database. Additionally, the SAP and TFL shells should be finalized prior to any programming activities commencing.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Amgen Inc. and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, ICH E9 guideline *Statistical Principles for Clinical Trials*.[1,2,3]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES

The primary objective of the study is:

- to evaluate the PK of AMG 592 after single subcutaneous (SC) administration in healthy Chinese, Japanese, and Caucasian subjects.

The secondary objectives of the study are:

- to evaluate the safety and tolerability of AMG 592 after single SC administration in healthy Chinese, Japanese, and Caucasian subjects.

- to evaluate the incidence of anti-AMG 592 and anti-IL-2 antibodies in healthy Chinese, Japanese, and Caucasian subjects after single SC administration of AMG 592.

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3. STUDY ENDPOINTS

The primary endpoints of the study are PK parameters for AMG 592:

- maximum observed serum concentration (C_{max})
- area under the serum concentration-time curve (AUC) from time zero to the last quantifiable concentration (AUC_{last})
- area under the serum concentration-time curve from time zero to infinity (AUC_{inf}).
- time of the maximum observed concentration (t_{max})

The secondary endpoints of the study are:

- treatment-emergent adverse events (AE) and serious adverse events (including clinical significant changes in physical examination [PE])
- clinical laboratory tests
- vital signs
- anti-AMG 592 and anti-IL-2 antibody formation

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4. STUDY DESIGN

This will be a Phase 1, single-center, open-label, sequential-group study to investigate the safety, tolerability, and PK of a single SC dose of AMG 592 in 2 groups of healthy Chinese subjects and 1 group of healthy Japanese subjects. In addition, a group of healthy Caucasian subjects will be evaluated at the high dose level for comparison.

Approximately 32 subjects will be enrolled in total, with CCI [redacted] subjects in each of the following 4 groups:

- Group 1: Chinese subjects (n=CCI [redacted]) will receive CCI [redacted] AMG 592 CCI [redacted] CCI [redacted] SC injection
- Group 2: Chinese subjects (n=CCI [redacted]) will receive CCI [redacted] AMG 592 CCI [redacted] CCI [redacted] SC injection

- Group 3: Japanese subjects (n=[redacted]) will receive [redacted]) SC injection
- Group 4: Caucasian subjects (n=[redacted]) will receive [redacted]) SC injection.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to dose administration.

Under the initial study design and plan prior to Amendment 2 of the protocol, [redacted] subjects in Group 1 and all subjects in Groups 3 and 4 had been enrolled, dosed, and had remained in the CRU up through the earliest discharge day on Day 3. Due to the occurrence of adverse events in subjects administered with AMG 592 reported thus far in the study after day 4 and during the period after discharge from the CRU, enrollment of the remaining [redacted] subjects in Group 1 was placed on temporary hold. The intention of the hold was to allow a full evaluation of emerging safety data and to prepare protocol amendment 2.

Under Protocol Amendment 2, the overall study design and plan will be conducted as follows, for the remaining [redacted] subjects in Group 1 (Chinese cohort, [redacted] and all subjects in Group 2 (Chinese cohort, [redacted]):

Eligible subjects will be admitted into the CRU for Check-in on Day -1 and be confined to the CRU until clinic discharge on Day 7. Individual subjects may be required to remain in the CRU for safety observations beyond Day 7 (to a maximum of Day 11) at the discretion of the Investigator, based on the emergence and progression of adverse events and other signs and symptoms requiring monitoring. Each subject will participate in 1 treatment group only.

Chinese subjects will be assigned to Group 1 or Group 2 in a sequential manner. Group 1 will be enrolled and dosed first, and will have postdose safety observations performed for at least 14 days prior to initiation of dosing in Group 2 to allow sufficient time for an adequate safety review.

A full review of all available safety and tolerability data from the study including Group 1 (Chinese cohort, [redacted]) will be performed by the Investigator and Sponsor to ensure it is safe to proceed with the planned dose escalation in Group 2 (Chinese cohort, [redacted]

Japanese and Caucasian subjects were assigned to Groups 3 and 4, respectively, according to the planned enrollment and study design prior to Amendment 2 of the protocol. Aside from the sequential conduct for Groups 1 and 2, there is no priority or required order for conduct of the different ethnic groups.

Serial blood samples will be collected for determination of AMG 592 serum concentrations, PK parameters, and PD markers.

For subjects to be enrolled under Amendment 2, after discharge from the CRU on Day 7, subjects will return for outpatient visits on Days 8, 11, 15, 22, 29, and the end of study (EOS) visit on Day 43. (For subjects enrolled prior to Amendment 2 and discharged on Day 3, outpatient visits also included Days 4, 5, and 6.) It is anticipated that many subjects will be

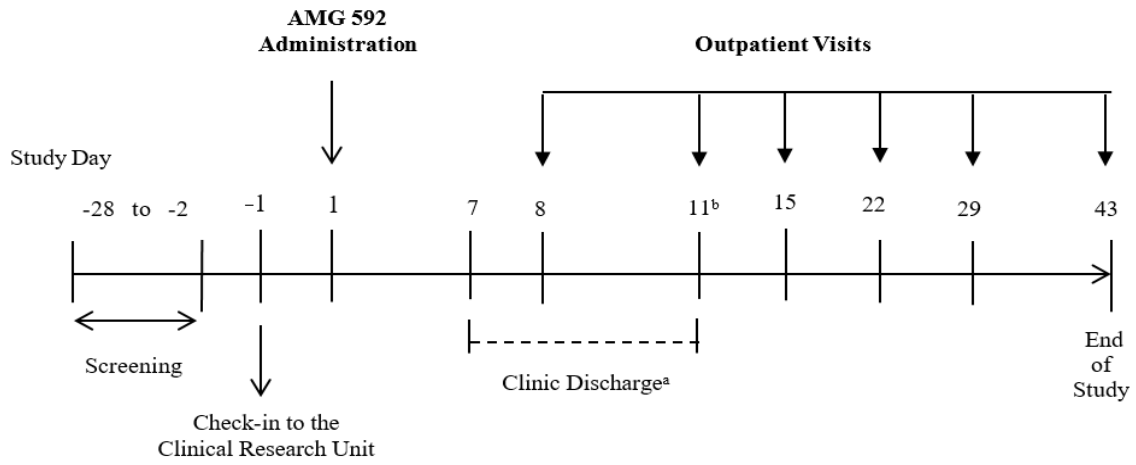
traveling a great distance to the CRU in order to participate in the study; therefore, to reduce unnecessary travel and ease the burden on subjects needing to find local accommodations for the frequent outpatient visits in the first 2 weeks of the study, subjects may reside in the CRU after clinic discharge on Day 7 through a maximum of Day 11. In addition to this elective option to remain in the CRU, individual subjects may be required to remain in the CRU beyond Day 7 (to a maximum of Day 11) at the discretion of the Investigator, based on the emergence and progression of adverse events or signs/symptoms of other adverse drug reactions. To summarize, a subject may leave the CRU after discharge procedures on Day 7, unless required to stay by the Investigator or, if not required to stay, may elect to stay voluntarily; in either case, residence in the CRU may be through a maximum of Day 11. Subjects who remain in the CRU beyond Day 7 will have the applicable scheduled outpatient procedures performed while resident. A subject's participation in the study will conclude at the completion of the EOS visit; however, subjects who test positive at EOS for neutralizing antibodies to IL-2 or binding antibodies with potentially antibody-mediated clinical sequelae will be asked to return for additional follow-up testing every 3 months until antibodies are no longer detected or up to 12 months (± 4 weeks) post administration of AMG 592 (whichever is shorter).

The total duration of study participation for each subject (from screening through the EOS visit) is anticipated to be approximately 10 weeks.

The start of the study is defined as the date the first subject signs an informed consent form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

An overview of the study design is shown in Figure 1.

Figure 1: Study Design



Note: Dashed line indicates that subjects may remain in the CRU beyond scheduled discharge on Day 7, as noted in footnote a. Outpatient visit procedures will be performed on an inpatient basis for subjects who are resident at the CRU on the scheduled outpatient visit days.

[a] The scheduled day of discharge is Day 7. Subjects may reside at the CRU after discharge on Day 7 until a maximum of Day 11, to reduce the travel and accommodation burden on subjects. In addition, the Investigator may require a subject to remain in the CRU after Day 7 (to a maximum of Day 11) based on the emergence and progression of adverse events or clinical signs and symptoms of adverse drug reaction. (For subjects enrolled prior to Amendment 2 of the protocol, the schedule day of discharge was Day 3.)
[b] The maximum planned in-clinic residence for a given subject is 12 days (Day -1 to Day 11), whether by subject choice for lodging and accommodation purposes or as required by the Investigator based on adverse event/s or clinical signs and symptoms of adverse drug reaction.

5. SAMPLE SIZE JUSTIFICATION

Approximately 32 subjects will be enrolled in 4 groups ([redacted] subjects per group).

With [redacted] subjects in each group receiving AMG 592, there is an [redacted] chance of [redacted] experiencing an adverse event with a true incidence rate of [redacted] chance of [redacted] experiencing an adverse event with [redacted] true incidence rate. With a total of 32 subjects expected to receive AMG 592 across 4 cohorts, there is a [redacted] chance of [redacted] experiencing an adverse event with a true incidence rate of [redacted] and the chance of [redacted] experiencing an adverse event increases to [redacted] with a true incidence rate of [redacted], respectively.

6. STUDY TREATMENTS

In addition to the 4 planned study treatments, an overall for [redacted] AMG 592 will also be presented in the TFLs. The study treatment names, abbreviations, and ordering to be used in the TFLs are presented in **Table 1**.

Table 1: Presentation of Study Treatment Groups in TFLs

Treatment Group	Order in TFLs
Chinese [redacted] AMG 592	1
Chinese [redacted] AMG 592	2
Japanese [redacted] AMG 592	3
Caucasian [redacted] AMG 592	4
Overall [redacted] AMG 592	5

7. DEFINITIONS OF POPULATIONS

Any protocol deviations, including those due to coronavirus disease 2019 (COVID-19) and related restrictions (see Section 8.1.1), will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

7.1. All Subjects Population

The all subjects population will include all subjects who signed the ICF and had any study assessment recorded in the database per the protocol.

7.2. Safety Population

The safety population will include all subjects who received at least 1 dose of AMG 592 and have at least 1 postdose safety assessment.

7.3. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of AMG 592 and have evaluable PK data.

7.4. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of AMG 592 and have evaluable PD data.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database, including medical history. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Subjects are generally considered to have completed the study if they complete the scheduled end of study visit (rather than early termination visit). Any subject who discontinues the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if a new version is issued during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if a new version is issued during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher if a new version is issued during the study). Pinnacle 21 Community (version 3.1.2 or higher) will be utilized to ensure compliance with CDISC standards.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to ‘valid’ data, this refers to non-missing data which meet the predetermined criteria (eg, are not flagged for exclusion).

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, changes from baseline, percentage changes from baseline, and any parameter derivations.

All figures will be produced on linear-linear or discrete-linear scales, as applicable, unless specifically stated otherwise.

8.1.1. Handling of Data Quality Issues Due to Coronavirus Disease 2019 and Related Restrictions

Due to COVID-19 and related restrictions, there is a high risk for impact to data integrity, with the recognized potential for:

- Missed visits, caused by, for example:
  - Subject unable to travel to site due to restrictions, the need to quarantine, or COVID-19 infection
  - Subject unwilling to go to site due to fear of COVID-19 infection
  - Site postponing subject's visit due to investigator not being available (eg, if they have been dispatched to hospital handling COVID-19 infections)
- Site unable to replenish supply of investigational product
- Incomplete data entry by sites due to limited resources to support study or no access to source documents or to eCRF
- Outstanding source document verification (SDV) due to sponsor or country restrictions on remote SDV, or no or limited access to site(s) for on-site visits
- Unanswered queries

At the time of the reporting of the study results, all protocol deviations due to COVID-19 or related restriction will be assessed for their severity and impact on the analyses. If needed, appropriate statistical methods will be applied as a mitigating action (eg, data might be categorized into 2 analysis groups, with and without COVID-19 and related restrictions impact); however, this will exclude any imputations of the missing values. Any mitigating actions will be agreed with Amgen Inc. in advance and identified in the CSR.

8.1.2. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.

- If the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- In general, as early termination data are not associated with any scheduled timepoint, they will be excluded from all calculations of summary statistics and statistical analyses. Exceptions may be made where justified.

For categorical data the following rules will be applied:

- For ordered categorical data (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category.
- For non-ordered categorical data (eg, race), only those categories for which there is at least 1 subject represented will be included; unless specifically stated otherwise.
- Missing values will not be imputed, unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

8.1.3. Repeat and Unscheduled Readings

For vital signs and 12-lead ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations, with the exception of the 12-lead ECG outlier analysis (see Section 8.7.4).

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see Section 8.1.4) and 12-lead ECG outlier analysis (see Section 8.7.4).

8.1.4. Definitions of Baseline, Change from Baseline, Percent Change from Baseline and Fold Change from Baseline

The baseline will be defined as the value recorded prior to dosing. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to dosing.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the postdose timepoint.

Fold Change from baseline = (Final Value / Baseline Value);

The summary statistics for change from baseline and fold changes from baseline will be derived from individual subjects' values (eg, mean change from baseline will be the mean of

the individual changes from baseline for all subjects, rather than difference between the mean value at the postdose timepoint and mean value at baseline).

See Section 8.1.3 for more detail on handling repeat and unscheduled readings in the calculations.

8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by treatment groups will be provided, based on the safety population.

8.3. Screening Demographics and Baseline Characteristics

The screening demographics and baseline characteristics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table by treatment groups will be provided, based on the safety population.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to dosing. Concomitant medication will be defined as medication that starts during or after dosing or starts but does not end prior to dosing.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version September 2020 (or later if a new version is issued during the study; see the data management plan [DMP] for more details). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the serum concentrations of AMG 592 using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

Parameter	Units[a]	Definition
AUC_{last}	hr*ng/mL	area under the concentration-time curve from time zero to time of last quantifiable concentration[b]
AUC_{inf}	hr*ng/mL	area under the concentration-time curve from time zero extrapolated to infinity[c]
$\%AUC_{extrap}$	%	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
C_{max}	ng/mL	maximum observed concentration
CL/F	L/hr	apparent total body clearance, calculated as Dose/AUC_{inf}
MRT_{inf}	hr	mean residence time observed from time zero to infinity

Vz/F	L	apparent volume of distribution based on the terminal phase, calculated as Dose/(AUC_{inf}*λz)
t_{max}	hr	time of maximum observed concentration
t_{last}	hr	time of the last quantifiable concentration
$t_{1/2}$	hr	apparent terminal elimination half-life

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] The area under the concentration-time curve will be calculated using the linear trapezoidal linear interpolation rule.
[c] Based on the last observed quantifiable concentration

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual dose administered (μg) and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

8.5.1.1. Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in concentrations.

The apparent terminal elimination rate constant (λ_z) will only be calculated when a reliable estimate can be obtained using at least 3 data points, preferably not including C_{max}, and the adjusted coefficient for determination of exponential fit (R^2-adj) of the regression line is ≥0.8. Parameters requiring λ_z for their calculation (eg, AUC_{inf}, and $t_{1/2}$) will only be calculated if the R^2-adj value of the regression line is ≥0.8.

The following regression-related diagnostic PK parameters will be determined, when possible:

Parameter	Units	Definition
λ_z	1/h	apparent terminal elimination rate constant
λ_z Upper	hr	end of exponential fit
λ_z Lower	hr	start of exponential fit
λ_z N	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2-adj	NA	adjusted coefficient for determination of exponential fit

Where possible, the span of time used in the determination of λ_z (ie, the difference between λ_z Upper and λ_z Lower) should be ≥2 half-lives. If the λ_z Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the clinical study report (CSR).

8.5.1.2. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

If the extrapolated area is >20%, AUC_{inf} (and derived parameters, CL/F and Vz/F) will be excluded from the summary statistics.

8.5.1.3. Criteria for Handling Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Serum concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK parameter analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a predose serum concentration is missing, it will be set to 0 by default within Phoenix WinNonlin.

8.5.1.4. Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be flagged in data listing and documented in the CSR.

Any quantifiable predose concentration value will be considered anomalous and set to missing for the PK analysis. This will be set to 0 by default in Phoenix WinNonlin.

8.5.2. Presentation of Pharmacokinetic Data

If the actual time of sample collection deviates from the nominal time by more than ±10%, the serum concentration will be flagged.

For serum concentration data the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.

For PK parameters the following rule will apply:

Geometric mean and coefficient of variation will not be calculated for t_{last} or t_{max}.

8.5.3. Pharmacokinetic Statistical Methodology

No inferential statistical analyses are planned.

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.7. Safety and Tolerability Assessments

8.7.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 (or higher if a new version is issued during the study; see the DMP for more details).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after dosing, or starts prior to dosing and increases in severity after dosing.

A treatment-related TEAE will be defined as a TEAE with a relationship related to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of dosing for TEAEs only.

The frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment

For the AE data the following rules will apply:

- For the derivation of treatment-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to not be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started after dosing.
- For the derivation of treatment-related status (applicable to TEAEs only): If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to not be a treatment-related TEAE.
- For the derivation of onset time (applicable to TEAEs only): If the start date/time of a TEAE is missing, onset time will not be calculated. If the start date/time of a TEAE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of dosing is 01MAY2019/08:00 and recorded start date/time of a TEAE is 03MAY2019, then the minimum possible onset time will be calculated by assuming a TEAE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing). If the start date of a TEAE is the same as the date of dosing but the start time of a TEAE is missing, an onset time will be presented as '≥00:00:01'. Any clock changes will be accounted for in the derivation.
- For the derivation of duration (applicable to all AEs): If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming an AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing). Any clock changes will be accounted for in the derivation.
- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category.
- For the calculation of TEAE summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

8.7.2. Clinical Laboratory Parameters

All clinical laboratory parameters, their changes from baseline, will be listed, as applicable; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

Summary tables and boxplots by treatment and timepoint will be provided by treatment group for clinical chemistry and hematology parameters, their changes from baseline, as applicable.

Values recorded as $<x$, $\leq x$, $>x$, or $\geq x$ will be displayed in the listings as recorded. For the derivation of listing flags, all calculations, and presentation in the figures, $<x$ and $\leq x$ values will be set to 0, whereas $>x$ and $\geq x$ values will be set to x.

8.7.3. Vital Signs Parameters

All vital signs parameters, their changes from baseline, will be listed, as applicable; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint will be provided by treatment group for all vital signs parameters, their changes from baseline, as applicable.

8.7.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters such as PR, QT and QTcF will be listed; any value outside the clinical reference range will be flagged.

8.7.5. Antibodies

The formation of anti-AMG 592 and anti-IL-2 antibodies will be summarized descriptively. The incidence and percentage of subjects who develop anti-AMG 592 antibodies and cross reactive anti-IL-2 antibodies (binding and if positive, neutralizing) will be summarized by treatment group. Furthermore, the incidence and percentage of subjects with treatment boosted anti-AMG 592 antibodies will also be summarized. In addition, subjects with positive binding and neutralizing anti-AMG 592 results will be listed individually with corresponding time points.

8.7.6. Other Assessments

Medical history will not be listed.

All other safety and tolerability assessments not detailed in the above sections will be listed only.

8.7.7. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No interim analyses are planned.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol-specified analyses.

11. REFERENCES

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12. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 3.0	NA	NA; the first version.

NA = not applicable