Statistical Analysis Plan

Protocol Title:	**A Randomized, Double-blind, Placebo-controlled Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Multiple Ascending Subcutaneous Doses of** AMG 592 in Subjects with Systemic Lupus Erythematosus
Short Protocol Title:	**Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Immunogenicity** of AMG 592 in Subjects with Systemic Lupus Erythematosus
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Version Number	**Date (DDMMMYYYY)**	**Summary of Changes, including rationale for changes**
Original	12 December 2017	NA
Amendment 1	01 December 2020	Changes related to protocol superseding amendment 5 (dated 25 June 2020)
Amendment 2	26 October 2021	Changes updated in definitions, statistical method of analyses and Appendix B
Amendment 3	**09 November 2021**	**Changes updated in laboratory test results and Appendix B**

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
Anti-dsDNA	Anti-double stranded DNA
AUC	area under the concentration-time curve
AUC_{tau}	area under the concentration-time curve over a dosing interval
BLRM	Bayesian logistic regression model
C_{max}	maximum observed concentration
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	case report form
CTCAE	common terminology criteria for adverse events
DLRM	dose level review meeting
ECG	Electrocardiogram
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
GSO-DM	The Amgen Global Study Operations-Data Management
IL-2	Interleukin 2
IP	Investigational Product
IPD	Important Protocol Deviations
IRT	interactive response technology that is linked to a central computer in real time as an interface to collect and process information
ISR	Injection Site Reaction
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NK cells	natural killer cells
PD	Pharmacodynamic
PK	Pharmacokinetic

PR Interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
QRS interval	QRS interval is the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a 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 ECG.
QTc interval	QT interval corrected for heart rate using accepted methodology
QW	every week
Q2W	every other week
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SC	Subcutaneous
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Tcon	conventional T cell
T_{max}	time of maximum observed concentration
TEAE	Treatment Emergent Adverse Events
Treg	regulatory T 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 superseding protocol amendment 5 for study 20170103, AMG 592 dated 25 June 2020. The scope of this plan includes the analysis for dose level review meetings (DLRM) and the final analysis that is 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/Estimands

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of subcutaneous (SC) dose administrations of AMG 592 in subjects with systemic lupus erythematosus (SLE)	• Treatment-emergent adverse events • Clinically significant changes in physical examinations, vital signs, and laboratory safety tests
Secondary	
• To characterize the pharmacokinetic (PK) profile following treatment with AMG 592	• AMG 592 serum concentration and PK parameters including, but not limited to, maximum observed concentration (Cmax), the time of maximum observed concentration (Tmax), and area under the concentration-time curve over a dosing interval (AUCtau) after the first and last doses
• To evaluate anti-AMG 592 antibody formation	• Incidence of anti-AMG 592 antibodies • Cross-reactivity of anti-AMG 592 antibodies with human interleukin-2 (IL-2) • Incidence of anti-AMG 592 and anti-IL 2 neutralizing antibodies
Exploratory	
• To explore the effect of treatment with AMG 592 on measures of inflammation at various time points	• Change from baseline in anti-double stranded DNA (anti-dsDNA), and C3 and C4 complements at all time points collected
• To explore the effect of treatment with AMG 592 on measures of disease activity at various time points	• SLEDAI-2K score and change from baseline at all time points collected
• To evaluate the immunological effects of AMG 592	• Fold changes from baseline of Treg, Tcon, and NK absolute cell counts (cells/µL) after AMG 592 administration • Changes in Treg/Tcon ratio after AMG 592 administration

2.2 Hypotheses and/or Estimations

AMG 592 will be safe and well tolerated in subjects with SLE. There is no formal hypothesis planned for the study.

3. Study Overview

3.1 Study Design

This phase 1b study is a double-blind, placebo-controlled, multiple ascending dose (MAD) study to evaluate the safety, tolerability, PK, immunogenicity**,** and PD of AMG 592 in subjects with SLE. 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.

Five dosing cohorts are planned for the study. For cohorts 1, 2, and 3, subjects within a dosing-cohort will be randomized in a 5:2 ratio to AMG 592 (n = 5) or placebo (n = 2) as follows: cohort 1 ([redacted] μg [redacted]); cohort 2 ([redacted] μg [redacted]); and cohort 3 ([redacted] μg [redacted]), in addition to standard of care therapy. For cohorts 4 and 5, subjects within a dosing-cohort will be randomized in a 3:1 ratio to AMG 592 (n = 3) or placebo (n = 1) as follows: cohort 4 ([redacted] μg [redacted]) and cohort 5 ([redacted] μg [redacted]), in addition to standard of care therapy. Dosing cohorts will enroll sequentially. A Dose Level Review Meeting (DLRM) will convene after the last subject in each cohort completes 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) if required will be implemented to model these events before each DLRM to aid dosing recommendations. Dose Level Review Meeting members will be responsible for dosing recommendations, which may include escalation to the next planned dose or a new higher 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. Dose Level Review Meeting members may also consider available aggregated summaries of emerging PK and PD data. Amgen DLRM members may consider safety, PK and PD data from other completed and ongoing phase 1b studies to aid dosing recommendations. Emerging safety, PK, and PD data from ongoing AMG 592 studies may be used to support recommendations to skip dosing cohorts, reduce dosing cohort size or change doses for a given cohort or stop the study entirely.

3.2 Sample Size

Within each cohort subjects will be randomized to AMG 592 or placebo in a 5:2 ratio for cohorts 1, 2 and 3 and in a 3:1 ratio for cohorts 4 and 5. It is planned that approximately 29 subjects will be enrolled with 7 subjects assigned to each cohort (5 to AMG 592 and 2 to placebo) for cohorts 1, 2 and 3 and 4 subjects assigned to cohorts 4 and 5 (3 to AMG 592 and 1 to placebo). The total sample size may exceed 29 subjects and the number of subjects within a cohort may exceed the planned cohort size if, following a DLRM recommendation, additional dosing cohorts are added and/or existing cohorts are expanded, or if subjects are replaced as per protocol Section 5.2.1. If additional subjects are added to a cohort the randomization ratio may not be preserved.

The sample size is based on practical considerations. With 5 subjects receiving AMG 592 per cohorts 1, 2, and 3, there is a 76% 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 67% if the event rate becomes 20%. With a total of 21 subjects planned to receive AMG 592 in the study, there is a 19% 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 66% if the true event rate becomes 5%.

4. Covariates and Subgroups

4.1 Planned Covariates

There are no pre-specified covariates.

4.2 Subgroups

There are no pre-specified subgroup analyses.

5. Definitions

5.1 Basic Definitions

Investigational Product (IP)

The term ‘investigational product’ is used in reference to AMG 592 all dose levels and placebo.

Prior Medication and Concomitant Medications

Prior medication is defined as any medication with start date prior to the first dose date of investigational product and ended before the 1st IP dose. Concomitant medication is defined as any medication with start date prior to the first dose date of investigational product but which continued to be taken after the first dose of investigational product or

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

5.2 Study Points of Reference

Baseline

For any variable, baseline is the last assessment taken prior to or on the first investigational product administration unless stated otherwise; for subjects who did not receive any investigational product, baseline is the last assessment on or before enrollment date.

Baseline for Pharmacodynamics (PD)

For lymphocyte subsets, if 2 or more time points are collected at day -1 and day 1 pre-dose, then the average of those time points will be reported.

Baseline medication

Baseline medication is defined as any medication with start date on or before Study Day 1 and ongoing while on study. If the medication is taken on the same day as the first dose and the exact time relative to the first dose is unknown, it will be assumed to have been taken prior to the first dose of IP.

Study Day

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

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

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

Study Day 1

Study day 1 is defined as the first day of administration of the investigational product or the day of enrollment if the subject does not receive any investigational product. The day prior to Study Day 1 is considered as Day -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 AMG592 or placebo through the IRT.

End of Investigational Product Date

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

Duration of Treatment-emergent Injection Site Reaction (ISR)

Duration = (min (ISR end date, EOS date) – ISR start date) + 1.

Duration of IP exposure

The duration of IP exposure will be derived as earliest date of the last IP administration plus <dosing frequency> -1, end of study, whichever occurs first, minus the date of first IP administration plus 1 day, where dosing frequency is 7 for QW dosing and 14 for Q2W dosing.

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 B.

5.3 Arithmetic Calculations

Change From Baseline

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

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.

Number of Days on Investigation Product

Number of days on IP is defined as last dose date – first dose date +1.

Treg to Tcon Ratio

The ratio is defined as number of Tregs divided by number of Tcons. When the value of Tcon is 0, then the ratio of Treg to Tcon is reported as 1.

5.4 Definitions of Study Endpoints

Systemic Lupus Erythematosus Disease Activity Index 2000

The SLEDAI-2K is a global index that evaluates disease activity and includes 24 items collecting specific manifestations in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular, and hematological. The maximum score is 105.

Incidence of Events of Interest

Incidents of events of interest such as selected adverse events or intolerable PD levels will be identified after safety data is collected and before each DLRM convenes.

Treatment-emergent Adverse Event (TEAE)

A treatment-emergent adverse event is any adverse event starting or worsening 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 last dose date or the End of Study date on eCRF form, whichever is earlier.

Treatment-related Adverse Event (TRAE)

A treatment-related AE is any treatment-emergent AE with the relationship flag on the Events eCRF indicating there is a reasonable possibility that the event may have been caused by investigational medicinal product. In the unlikely event that the relationship is missing, the treatment-emergent event will be considered treatment-related and documented in a footnote of the treatment-related summary.

Disease-related Event

Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available.

Disease-related events that would qualify as an adverse event or serious adverse event:

An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

Disease-related events that do not qualify as adverse events or serious adverse events:

An event which is part of the normal course of disease under study (e.g., disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

Disease-related events pre-defined for this study include: lupus-related joint pain, joint stiffness, joint swelling, rash, alopecia, and mucosal ulcers.

5.5 Demographic and Characteristics

Age

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

6. Analysis Sets

6.1 Safety Analysis Set

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

6.2 Pharmacokinetic Concentration Analysis Set

The PK concentration analysis set will contain all subjects who have received AMG 592 and have at least one reported PK concentration.

6.3 Pharmacokinetic Parameter Analysis Set

The PK parameter analysis set will consist of all subjects who have received AMG 592 and for whom at least one PK parameter can be adequately estimated.

6.4 Pharmacodynamic Analysis Sets

The PD analysis set will consist of all subjects who have received AMG 592 or placebo, and for whom at least 1 PD parameters has a quantifiable baseline sample and at least one quantifiable post-baseline PD sample has been collected.

7. Planned Analyses

7.1 DLRMs

The study will have DLRMs for each cohort after the last subject in the cohort completes week 4 visit. Section 3.1 details the timings and scope of each DLRM planned for the study.

All available data the subjects up to and including the data snapshot date will be included in the analysis based on an “as-is” snapshot of the database without data locking. Data will be subject to ongoing checks for integrity, completeness and accuracy in accordance with the Data Management Plan; however, there is no requirement to resolve outstanding data issues ahead of the DLRM snapshot. DLRM analysis will include subject-level listings and plots of available safety data (labs, and vitals) for each

cohort and the BLRM analysis if required. The recommendations for dose escalation/dose modifications will be based on the DLRMs.

7.2 Final Analysis

The final analysis will be done after all subjects have completed the study (i.e., the safety follow-up visit). Final lock for the study will be performed at this point and the study will be unblinded. All outstanding data issues will be resolved ahead of the final lock. All study data will be included in the clean snapshot of the database after the final data lock. All analyses described in this analysis plan will be performed as part of final analysis. Results from these analyses will be included in the Clinical Study Report.

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. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

All endpoints in the study will be analyzed as-is and no imputation is planned.

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 for this study.

8.7 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.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, PD, immunogenicity, efficacy**,** and biomarker data. Descriptive statistics on continuous measurements will include means, medians, Q1, Q3, standard deviations, standard errors and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be presented and summarized by treatment and also by time as appropriate.

For the DLRM analyses safety data will be listed and figures may be provided. The scope of review includes all available study data including demographics, medical history, concomitant therapies, adverse events, electrocardiograms, vital signs, laboratory results, and emerging pharmacokinetic and pharmacodynamics data.

9.2 Subject Accountability

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 dose cohort.

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

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 Summary of IPDs table and the List of Subjects with IPDs.

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

The number of subjects with important protocol deviations and protocol deviations due to COVID-19 will be summarized in a table. A list of important protocol deviations and protocol deviations for subjects impacted by COVID-19 will also be provided.

9.4 Demographic and Baseline Characteristics

9.4.1 Demographic

- Age (years) at enrollment (continuous summary statistics)
- Age in categories (number and percentage of 18 – 64, 65 – 74, 75 – 84, ≥ 85 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, weight and Body Mass Index (BMI) (continuous summary statistics)
- Baseline SLEDAI-2K score (number and percentage of 0 to 5**,** 6 to 9, ≥ 10)
- Subject incidence (number and percentage) of baseline corticosteroids and baseline SLE-related medication

9.5 Efficacy Analyses

9.5.1 Analyses of Exploratory Efficacy Endpoint (s)

The SLEDAI-2K total score and change from baseline will be provided at all time points collected.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

The primary endpoint of this study is safety. The analysis will include the descriptive summary statistics for adverse events, disease-related events, laboratory measures, vital signs, physical measurements. Details are described in respective section below. Safety analysis set will be used for analyses included in this section.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later will be used to code all events categorized as adverse events, all disease-related events to a system organ class and a preferred term. The severity of each adverse event will be graded using CTCAE criteria version 4.03.

Subject incidence of all treatment-emergent, serious treatment-emergent, treatment-related, serious treatment-related, disease-related treatment-emergent, those leading to withdrawal from investigational product, and fatal adverse events will be tabulated by system organ class in alphabetical order, preferred term and grade in descending order of frequency. Subject incidence of treatment-emergent adverse events identified by

COVID-19 standardized MedDRA queries and serious adverse events occurring on or after the COVID-19 infection will also be summarized.

Subject incidence of treatment-emergent events of interest (standardized MedDRA queries and/or Amgen Medical Queries) will also be summarized according to their categories, preferred term, and worst severity grade. Events of interest could include but are not limited to Hypersensitivity, Tachyarrhythmias, Tachypnea, Hematopoietic Cytopenia, Drug Reaction with Eosinophilia, Leucocyte Changes, Infection and Infestation, Cytokine Release Syndrome, and Injection Site Reaction. Number of episodes and duration of treatment-emergent injection site reactions will be further summarized by treatment group.

9.6.3 Laboratory Test Results

The laboratory analytes listed below in the Table 9-1 will be analyzed. Unscheduled assessments **(Appendix B)** will be incorporated in the laboratory analyses where possible.

For chemistry and hematology lab analytes, the analyses of safety laboratory endpoints will include summary statistics of baseline, post-baseline values at all time points, change from baseline to post-baseline values at all time points, post-baseline maximum/minimum and change from baseline to post-baseline maximum/minimum by treatment group**.** Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated **based on CTCAE version 4.03**. **Subject incidence of worst post-baseline level of eosinophils counts by the laboratory normal range will be tabulated by treatment group.**

The urine protein analyte in the urinalysis will be graded in the following manner: Negative, Trace, 1+, 2+, 3+, 4+. The number and percent of subjects in these categories at all time points will be presented.

Table 9-1. Analyte Listing

Chemistry	Hematology	Urinalysis
Sodium	Red blood cells	Urine protein
Potassium	Antinuclear antibody	
Chloride	Hemoglobin	
Bicarbonate	Hematocrit	
Total protein	Mean corpuscular volume (MCV)	
Albumin	Mean corpuscular hemoglobin (MCH)	

Calcium	Mean corpuscular hemoglobin concentration (MCHC)	
Magnesium	Red cell distribution width (RDW)	
Phosphorus	Reticulocytes	
Glucose	Platelets	
BUN or Urea	White blood cells	
Creatinine		
Total bilirubin		
Direct bilirubin		
Alkaline Phosphatase (ALP)		
Aspartate Aminotransferase (AST) (Serum Glutamic-Oxaloacetic Transaminase (SGOT))	WBC Differential • Total neutrophils or segmented neutrophils • Bands/stab • Eosinophils • Basophils • Lymphocytes • Monocytes	
Alanine Aminotransferase (ALT) (Serum Glutamic-Pyruvic Transaminase (SGPT))		

9.6.4 Vital Signs

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

9.6.5 Physical Measurements

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

9.6.6 Electrocardiogram

The ECG measurements will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, summaries and statistical analyses of ECG

measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.7 Antibody Formation

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.

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group. The number of days on investigational product and the total dose of investigational product will be summarized using descriptive statistics. Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.

Descriptive statistics of the total dose, **number of doses received,** duration of usage, **and** number and percentage of subjects with **number of doses received**, dose change/withheld and reasons for dose change/withheld will be summarized. **Number and percentage of subjects with** missed IP doses due to COVID-19 will be also summarized.

A listing of the unique manufacturing lot numbers and a listing of the subjects administered by each manufacturing lot number will be provided.

9.6.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug dictionary.

9.7 Other Analyses

Secondary endpoints in study include PK endpoints and immunogenicity endpoints. Exploratory endpoints in this study include biomarker endpoints, efficacy endpoint and PD endpoints.

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

9.7.1.1 Analysis of Pharmacokinetic Endpoint

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. Serum concentrations of AMG592 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.

From the serum concentration-time data, the following PK parameters will be determined, as data permit: maximum observed concentration (Cmax), the time of maximum observed concentration (Tmax), and area under the concentration-time curve over a dosing interval (AUCtau) after the first and last doses.

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 by treatment group. Analyses will be conducted by Amgen Clinical Pharmacology Modeling and Simulation (CPMS).

9.7.1.2 Analysis of Pharmacodynamic Endpoints

The pharmacodynamic analysis set defined in Section 6 will be used. PD assessments include but are not limited to:

- Regulatory T cells (Treg), Conventional T cells (Tcon), CD8 T cells and Natural Killer (NK) absolute cell counts and percentages
- Treg/Tcon ratio

Fold changes from baseline in the above PD assessments at all time points will be summarized by treatment group. Furthermore, the mean (+/- standard error) of fold changes from baseline will be plotted for each treatment group at all time points. Due to the skewed distribution of PD data, the mean, standard deviation and standard error will

be estimated based on log-transformed data, and the estimates will be back-transformed and presented, which are equivalent to the geometric mean, geometric standard deviation and geometric standard error respectively.

To maintain the integrity of PD results, data collected at an early termination visit which is completed outside the protocol defined window (> 9 days after the last dose date for QW cohorts and > 16 days for Q2W cohorts) will not be included in the analysis. In addition, data collected at a visit after skipping one or more consecutive doses prior to the visit will be also excluded.

9.7.2 Analyses of Biomarker Endpoints

Absolute and change from baseline in anti-double stranded DNA (anti-dsDNA), and C3 and C4 complements at all time points will be summarized by treatment group.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

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12. Appendices

Appendix A. Concomitant Medications/Adverse Event Missing Value Imputation

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. Analytical Windows

The last measurement for the endpoint of interest taken prior to or on the first dose of investigational product in this study, unless stated otherwise 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, post-dose assessments on Day 85 (the day corresponding to week 12 dosing) and assessments at Safety follow-up/EOS visit, 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 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 are 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 pharmacodynamics 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 actual study day when Week 12 dose was received. If that dose is missing, then target Day 85 is used for the calculation.

Vital Sign

Analysis Visit	Target Day	Start Day	End Day
Week 1, Day 2	2	2	2
Week 1, Day 3	3	3	3
Week 1, Day 4	4	4	6
Week 1, Day 8	8	7	9
Week 1, Day 11	11	10	12
Week 2, Day 15	15	13	19

Week 3, Day 22	22	20	26
Week 4, Day 29	29	27	33
Week 5, Day 36	36	34	40
Week 6, Day 43	43	41	47
Week 7, Day 50	50	48	54
Week 8, Day 57	57	55	61
Week 9, Day 64	64	62	68
Week 10, Day 71	71	69	75
Week 11, Day 78	78	76	'Day 85' - 1
Week 12, Day 85	85	'Day 85'	
Week 12, Day 86	86	'Day 85' + 1	'Day 85' + 1
Week 12, Day 87	87	'Day 85' + 2	'Day 85' + 2
Week 12, Day 88	88	'Day 85' + 3	'Day 85' + 3
Week 13, Day 92	92	'Day 85' + 4	96
Week 14, Day 99	99	97	106
Week 16, Day 113	113	107	120
Week 18 (SFU), Day 127	127	>120	

Chemistry

Analysis Visit	Target Day	Start Day	End Day
Week 4, Day 29	**29**	**2**	**43**
Week 8, Day 57	**57**	**44**	**71**
Week 12, Day 85 Pre-Dose	**85**	**72**	**'Day 85'**
Week 18 (SFU), Day 127	**127**	**>'Day 85'**	

Hematology

Analysis Visit	Target Day	Start Day	End Day
Week 1, Day 2	2	2	3
Week 2, Day 15	15	4	22
Week 4, Day 29	29	23	36
Week 6, Day 43	43	37	50
Week 8, Day 57	57	51	64
Week 10, Day 71	71	65	78

Week 12, Day 85 Pre-Dose	85	79	'Day 85'
Week 14, Day 99	99	'Day 85' + 1	106
Week 16, Day 113	113	107	120
Week 18 (SFU), Day 127	127	>120	

Urinalysis

Analysis Visit	Target Day	Start Day	End Day
Week 4, Day 29	**29**	**2**	**43**
Week 8, Day 57	**57**	**44**	**71**
Week 12, Day 85 Pre-Dose	**85**	**72**	**'Day 85'**

Weight

Analysis Visit	Target Day	Start Day	End Day
Week 12, Day 85 Pre-Dose	85	**2**	'Day 85'
Week 18 (SFU), Day 127	127	**>'Day 85'**	

Pharmacodynamic Assessments

Analysis Visit	Target Day	Start Day	End Day
Week 1, Day 2	2	2	2
Week 1, Day 4	4	3	6
Week 1, Day 8	8	7	9
Week 1, Day 11	11	10	12
Week 2, Day 15	15	13	19
Week 3, Day 22	22	20	26
Week 4, Day 29	29	27	33
Week 5, Day 36	36	34	40
Week 6, Day 43	43	41	47
Week 7, Day 50	50	48	54
Week 8, Day 57	57	55	61
Week 9, Day 64	64	62	68
Week 10, Day71	71	69	75
Week 11, Day 78	78	76	82

Week 12, Day 85 Pre-dose	85	83	'Day 85'
Week 13, Day 92	92	'Day 85' +1	96
Week 14, Day 99	99	97	106
Week 16, Day 113	113	107	120
Week 18 (SFU), Day 127	127	>120	

Antibody Assessments

Analysis Visit	Target Day	Start Day	End Day
Week 2, Day 15	15	2	22
Week 4, Day 29	29	23	43
Week 8, Day 57	57	44	71
Week 12, Day 85 Pre-Dose	85	72	'Day 85'
Week 18 (SFU), Day 127	127	>'Day 85'	

Efficacy assessments (SLEDAI-2K)

Analysis Visit	Target Day	Start Day	End Day
Week 4, Day 29	29	**2**	43
Week 8, Day 57	57	44	71
Week 12, Day 85 Pre-Dose	85	72	'Day 85'

Anti-double stranded DNA

Analysis Visit	Target Day	Start Day	End Day
Week 1, Day 8	8	2	15
Week 4, Day 29	29	16	43
Week 8, Day 57	57	44	71
Week 12, Day 85 Pre-Dose	85	72	'Day 85'
Week 18 (SFU), Day 127	127	>'Day 85'	

C3 and C4 Complement

Analysis Visit	Target Day	Start Day	End Day
Week 1, Day 8	8	2	15
Week 4, Day 29	29	16	43
Week 8, Day 57	57	44	71
Week 12, Day 85 Pre-Dose	85	72	'Day 85'
Week 18 (SFU), Day 127	127	>'Day 85'	

Appendix C. Summary of Changes and Rationale for Change to the SAP Amendment 3

The statistical analysis plan for this study was amended to reflect the changes in laboratory test results and Appendix B. Editorial changes and minor clarifications were also implemented throughout the document.

Description of Changes

Global

Header date was replaced with 09 November 2021.

9. Statistical Methods of analysis

9.6.3 Laboratory Test Results

Removed:

Individual chemistry and hematology laboratory data will be listed. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. CTCAE grades will also be highlighted where appropriate

Added:

The urine protein analyte in the urinalysis will be graded in the following manner: Negative, Trace, 1+, 2+, 3+, 4+. The number and percent of subjects in these categories at all time points will be presented.

Revised:

For chemistry and hematology lab analytes, the analyses of safety laboratory endpoints will include summary statistics of baseline, post-baseline values at all time points, change from baseline to post-baseline values at all time points, post-baseline maximum/minimum and change from baseline to post-baseline maximum/minimum by treatment group**.** Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated **based on CTCAE version 4.03**. **Subject incidence of worst post-baseline level of eosinophils counts by the laboratory normal range will be tabulated by treatment group.**

Table 9-1. Analyte Listing

Chemistry	Hematology	Urinalysis
Sodium	Red blood cells	Urine protein
Potassium	Antinuclear antibody	
Chloride	Hemoglobin	
Bicarbonate	Hematocrit	
Total protein	Mean corpuscular volume (MCV)	
Albumin	Mean corpuscular hemoglobin (MCH)	
Calcium	Mean corpuscular hemoglobin concentration (MCHC)	
Magnesium	Red cell distribution width (RDW)	
Phosphorus	Reticulocytes	
Glucose	Platelets	
BUN or Urea	White blood cells	
Creatinine		
Total bilirubin		
Direct bilirubin		
Alkaline Phosphatase (ALP)		
Aspartate Aminotransferase (AST) (Serum Glutamic-Oxaloacetic Transaminase (SGOT))	WBC Differential • Total neutrophils or segmented neutrophils • Bands/stab • Eosinophils • Basophils • Lymphocytes • Monocytes	
Alanine Aminotransferase (ALT) (Serum Glutamic-Pyruvic Transaminase (SGPT))		

9.6.8 Exposure to Investigational Product

Revised:

Descriptive statistics of the total dose, **number of doses received,** duration of usage, and number and percentage of subjects with **number of doses received**, dose change/withheld and reasons for dose change/withheld will be summarized. **Number and percentage of subjects with** missed IP doses due to COVID-19 will be also summarized.

12. Appendices

Appendix B. Analytical Windows

Removed:

ECG

Analysis Visit	Target Day	Start Day	End Day
Week 1, Day 2	2	2	3
Week 1, Day 8	8	4	12
Week 2, Day 15	15	13	22
Week 4, Day 29	29	23	36
Week 6, Day 43	43	37	50
Week 12, Day 86	86	51	91
Week 14, Day 99	99	92	106
Week 16, Day 113	113	107	120
Week 18 (SFU), Day 127	127	>120	

Added:

Chemistry

Analysis Visit	Target Day	Start Day	End Day
Week 4, Day 29	**29**	**2**	**43**
Week 8, Day 57	**57**	**44**	**71**
Week 12, Day 85 Pre-Dose	**85**	**72**	**'Day 85'**
Week 18 (SFU), Day 127	**127**	**>'Day 85'**	

Urinalysis

Analysis Visit	Target Day	Start Day	End Day
Week 4, Day 29	**29**	**2**	**43**
Week 8, Day 57	**57**	**44**	**71**
Week 12, Day 85 Pre-Dose	**85**	**72**	**'Day 85'**

Revised:

Hematology

Analysis Visit	Target Day	Start Day	End Day
Week 1, Day 2	2	2	3
Week 2, Day 15	15	4	22
Week 4, Day 29	29	23	36
Week 6, Day 43	43	37	50

Weight

Analysis Visit	Target Day	Start Day	End Day
Week 12, Day 85 Pre-Dose	85	**2**	'Day 85'
Week 18 (SFU), Day 127	127	**>'Day 85'**	

Efficacy assessments (SLEDAI-2K)

Analysis Visit	Target Day	Start Day	End Day
Week 4, Day 29	29	**2**	43
Week 8, Day 57	57	44	71
Week 12, Day 85 Pre-Dose	85	72	'Day 85'