Protocol

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

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Investigational Product: AMG 592 (efavaleukin alfa)

Amgen Protocol Reference Number: 20200102
Labcorp Drug Development Study Number: 8448873
IND Number: 131270

Sponsor:
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INVESTIGATOR AGREEMENT

I have read the protocol entitled "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," and agree to conduct the study as described herein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____

Signature

_____ _____

PPD Date (DD Month YYYY)

STUDY IDENTIFICATION

Sponsor	Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320
Sponsor's Study Contact	PPD
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SYNOPSIS

Title of study: 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

Objectives:

The primary objective of the study is:

- to evaluate the pharmacokinetics (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-interleukin (IL)2 antibodies in healthy Chinese, Japanese, and Caucasian subjects after single SC administration of AMG 592.

CCI [redacted]

Study design:

This will be an open-label, single-dose, sequential-group study in 2 groups of healthy Chinese subjects and 1 group of Japanese subjects. In addition, a group of Caucasian subjects will be evaluated at the high dose for comparison. Potential subjects will be screened within 28 days prior to the dose.

Under the initial study design and plan prior to Amendment 2 of the protocol, CCI subjects in Group 1 (Chinese cohort, CCI) and all subjects in Groups 3 and 4 (Japanese and Caucasian cohorts, respectively, CCI) had been enrolled, dosed, and had remained in the clinical research unit (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 CCI 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 (to be conducted for the remaining CCI subjects in Group 1 [Chinese cohort, CCI] and all subjects in Group 2 [Chinese cohort, CCI], eligible subjects will be admitted into the CRU on Day 1 and will be confined to the CRU until discharge on Day 7 (individual subjects may be required to stay longer than Day 7 [to a maximum of Day 11] at the request of the Investigator based on emergence and progression of adverse events or other signs and symptoms requiring monitoring). The clinical conduct for the 2 groups of Chinese subjects will be done in a sequential manner, such that Group 1 will be enrolled and dosed first, with a postdose safety evaluation period of at least 14 days prior to initiation of dosing in Group 2. Chinese subjects (n = CCI/group) will receive a single SC dose of AMG 592 at CCI (Group 1) or CCI (Group 2). Since Protocol Amendment 1, Japanese subjects (n = CCI) received a single SC dose of AMG 592 at CCI (Group 3), Caucasian subjects (n = CCI) received a single SC dose of AMG 592 at CCI (Group 4), and Chinese subjects (n=CCI) received a single SC dose of AMG 592 at CCI (Group 1). After discharge from the research facility on Day 7, subjects will return to the CRU for outpatient visits on Days 8, 11, 15, 22, 29, and at 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.) A subject's participation in the study will conclude at the completion of the EOS visit; however, subjects who test positive at the EOS timepoint for neutralizing antibodies to IL2 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 from dosing (whichever is shorter).

Number of subjects:

Approximately 32 subjects (CCI per group) will be enrolled in this study.

Diagnosis and main criteria for inclusion:
Healthy male or female subjects of Chinese ancestry, first- or second-generation Japanese subjects, and Caucasian subjects, 18 to 55 years of age (inclusive), body mass index of 17 to 30 kg/m^2 (inclusive).

Investigational products, dose, and mode of administration:
Investigational Medicinal Product: CCI AMG 592 given as a CCI SC injection, CCI AMG 592 given as a CCI SC injection.
Group 1 = CCI SC
Group 2 = CCI SC
Group 3 = CCI SC
Group 4 = CCI SC

Duration of subject participation in the study:
Planned Screening duration: approximately 4 weeks.
Planned study duration (Screening to EOS): approximately 10 weeks.

Primary endpoints:
The primary endpoints for this study are PK parameters: maximum observed serum concentration (C_{max}), the time of maximum observed serum concentration (t_{max}), area under the serum concentration-time curve (AUC) from time zero to time of last quantifiable concentration (AUC_{last}), and AUC from time zero to infinity (AUC_{inf}).

Secondary endpoints:
Secondary endpoints for this study are: treatment-emergent adverse events and serious adverse events (including clinically significant changes in physical examinations), clinical laboratory tests, vital signs, and anti-AMG 592 and anti-IL-2 antibody formation.
CCI

Statistical methods:
Data will be analyzed for all subjects who were enrolled and received a dose of AMG 592. Descriptive statistics by treatment arm will be provided for selected demographics, safety, PK parameters, and PD and immunogenicity data. Descriptive statistics on continuous measurements will include geometric and arithmetic means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. The PK, vital signs, and clinical laboratory data will be summarized for each timepoint when samples are collected.
The final safety analysis for the study will be performed at the end of the study. Adverse events will be summarized using descriptive methodology. Each adverse event will be coded using the Medical Dictionary for Regulatory Activities. No imputation will be done for safety assessments, and endpoints for clinical laboratory tests and vital signs will be summarized. No inferential statistical analysis is planned.
Additional details will be included in the Statistical Analysis Plan.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC_{inf}	area under the serum concentration-time curve from time zero to infinity
AUC_{last}	area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AV	atrioventricular
BP	blood pressure
CD4	cluster of differentiation 4
CD25	alpha chain of the interleukin 2 receptor
CFR	Code of Federal Regulations
C_{max}	maximum observed serum concentration
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CRU	clinical research unit
DILI	drug-induced liver injury
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
FIH	first-in-human
FOXP3	forkhead box P3; an essential transcription factor of Treg function, upregulated by IL-2R signals
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GvHD	graft-versus-host disease
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IL	interleukin
IL-2R	interleukin 2 receptor
IL-2RA	interleukin 2 receptor alpha chain
IL-2RB	interleukin 2 receptor beta chain
ILC2	innate lymphoid cells
IMP	investigational medicinal product
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	institutional review board

IUD	intrauterine device
NK	natural killer
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic
PE	physical examination
PK	pharmacokinetic(s)
Q2W	every 2 weeks
QTcF	QT interval corrected for heart rate using Fridericia's method
QW	once weekly
RA	rheumatoid arthritis
SC	subcutaneous
SLE	systemic lupus erythematosus
$t_{1/2}$	terminal elimination half-life
TB	tuberculosis
TBL	total bilirubin
Tcon	conventional T cells
t_{max}	time of the maximum observed serum concentration
Tregs	regulatory T cells
ULN	upper limit of normal

1. INTRODUCTION

Refer to the Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational medicinal product (IMP).

1.1. Background

Investigational Medicinal Product

Regulatory T cells (Tregs) are a subset of cluster of differentiation 4 (CD4) T cells that suppress inflammation and whose numbers and function are maintained by interleukin (IL)-2. In addition to Treg, IL-2-responsive lymphocytes include conventional CD4 and CD8 T (Tcon) cells, natural killer (NK) cells, and innate lymphoid cells (ILC2). A loss in the homeostatic balance between Tregs and other lymphocytes is considered a causative factor in many inflammatory conditions.

AMG 592 (efavaleukin alfa) is an Fc-IL-2 mutein that contains 2 mutations in the IL-2 domain. To increase the Treg selectivity of IL-2, 1 mutation is in the region that binds the beta chain of the IL-2 receptor (IL-2RB). This mutation reduces its signaling potency and increases its dependence on expression of interleukin 2 receptor alpha chain (IL-2RA/CD25). It drives a positive feedback loop enforcing Treg phenotype, abundance, and IL-2 responsiveness over effects on other lymphocytes. The other mutation is in an internal region of IL-2 and improves manufacturability of AMG 592 but does not alter its biological activity.[2,3,4]

The IL-2R is composed of 3 chains: IL-2RB and IL-2R gamma, which together deliver the intracellular IL-2R signal, and IL-2RA (CD25), which stabilizes IL-2 association with IL-2RBG but does not contain a signaling domain. The alpha chain of the IL-2 receptor (CD25) is highly expressed on Treg, and IL-2R signaling in Treg promotes expression of both CD25 and FOXP3, the essential transcription factor for Treg development and function. High FOXP3 expression promotes both full Treg suppressor activity and high CD25 expression, resulting in a positive feedback loop enforcing Treg phenotype, abundance, and IL-2 responsiveness.[2,3,4]

The mutation in the IL-2RB-binding region of IL-2 results in increased dependence on CD25 for IL-2R signaling compared with wild-type IL-2. Thus, efavaleukin alfa preferentially drives this positive feedback loop in Treg over effects on other lymphocytes (ie, other T cells and ILC2 which may express CD25 but do not express FOXP3, and NK cells which express little or no CD25 and no FOXP3). Compared with aldesleukin, efavaleukin alfa exhibits greatly improved selectivity for Treg over Tcon and NK cells both in vitro and in vivo, potentially resulting in an improved therapeutic margin. In addition, the Fc domain of AMG 592 confers a prolonged half-life compared with aldesleukin, thus reducing the dosing frequency required to maintain Treg enrichment

Nonclinical in vitro and in vivo studies have demonstrated that AMG 592 exhibits greater selectivity for inducing Treg expansion over the expansion of CD4 and CD8 T cells, and NK cells, relative to low dose, recombinant IL-2. This greater selectivity of AMG 592 has promise for greater efficacy and a wider therapeutic margin in inflammatory diseases relative to low-dose recombinant IL-2-based modalities.

Amgen is developing AMG 592 as a treatment for multiple inflammatory diseases including systemic lupus erythematosus (SLE), steroid-refractory chronic graft-versus-host disease (GvHD), and ulcerative colitis. This study is designed to evaluate whether pharmacokinetic (PK) and safety data in Chinese and Japanese subjects are similar to those from the global population.

A summary of completed and ongoing clinical studies for AMG 592 is provided in the IB.[1]

Changes to Study Protocol 20200102 (Amendment 1)

Under the study design and planning in Amendment 1, subjects in Group 1, Group 3, and Group 4 had been enrolled, dosed, and had remained in the clinical research unit (CRU) up through the earliest discharge day on Day 3. Due to the occurrence of adverse events in subjects administered with AMG 592 thus far in the study after day 4 and during the period after discharge from the CRU, enrollment of the remaining CCI 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. The remaining CCI subjects in Group 1 (Chinese cohort, CCI) and all subjects in Group 2 (Chinese cohort, CCI) will be enrolled under the amended protocol (Protocol Amendment 2).

1.2. Pharmacokinetics

In a first-in-human (FIH) study (Study 20140324), PK results of AMG 592 in healthy subjects following single-dose subcutaneous (SC) administration of AMG 592 are available for doses of CCI . Results show dose-related increases in AMG 592 serum exposure (as assessed by maximum observed concentration [C_{max}] and area under the serum concentration-time curve [AUC] from time zero to infinity [AUC_{inf}]) with approximately dose-proportional increase over the CCI CCI . Following SC administration, the median time to maximum observed serum concentration (t_{max}) ranged from approximately 0.5 to 1 day with terminal phase half-life ($t_{1/2}$) about 11 to 13 hours postdose at doses CCI .

In a single-dose PK study in healthy Japanese subjects (Study 20180132), exposure of AMG 592, assessed by C_{max} and AUC_{inf}, increased approximately dose proportionally over the CCI . Mean C_{max} and AUC_{inf} exhibited CCI . The median t_{max} was 14 hours in the AMG 592 CCI cohort and 24 hours in the AMG 592 CCI cohort. For the CCI cohort, the mean half-life, apparent drug clearance, volume of distribution, and mean residence time was 11.7 hours, 1.29 L/hour, 21.9 L, and 33.2 hours, respectively. For the CCI cohort, the mean half-life, apparent drug clearance, volume of distribution, and mean residence time was 9.68 hours, 0.852 L/hour, 11.7 L, and 39.5 hours, respectively.

In a multiple-dose study in patients with active rheumatoid arthritis (RA), exposure to AMG 592, as expressed in AUC and C_{max}, increased with increasing dose from CCI every 2 weeks (Q2W) to CCI once weekly (QW) to CCI Q2W. Peak concentrations were observed about 6 to 12 hours following dosing, with half-lives that ranged from about 10 to 40 hours. Moderate drug accumulation was observed for

CCI Q2W and CCI QW. There were not enough data to determine the accumulation ratio for the CCI Q2W dose.

1.3. Study Rationale

The highest dose of AMG 592 previously evaluated in healthy Japanese and Caucasian subjects is CCI and a dose of CCI has demonstrated Treg selectivity and acceptable safety in subjects with SLE. As AMG 592 has not previously been studied in healthy Chinese subjects, CCI was chosen as the low-dose level to permit direct comparison with results from previous studies. Chinese, Japanese, and Caucasian subjects were selected in order to allow comparison to previous data and extrapolation to future studies, to look for possible ethnic variation in PK or PD parameters, and as part of the effort to ensure that proper dose regimens are recommended for the appropriate patient populations of different ethnicities. The current study should inform dose selection and design of future Phase 2 and 3 studies.

1.4. Benefit-risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study. Refer to the IB[1] for more information.

1.4.1. Therapeutic Context

1.4.1.1. Benefits

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study.

1.4.1.2. Risks

The safety of AMG 592 (efavaleukin alfa) has been studied in healthy volunteers and in SLE, chronic GvHD, and RA patients. Prior to the current study, approximately 136 subjects have been exposed to efavaleukin alfa in Amgen clinical studies. Single SC doses of up to CCI of efavaleukin alfa have been studied in healthy volunteers. Repeated SC doses of up to CCI of efavaleukin alfa administered Q2W have been studied in subjects with chronic GvHD over the course of a 52-week period. Doses up to CCI Q2W have been studied in subjects with SLE and up to CCI in subjects with RA over the course of a 12-week period. The safety profile of efavaleukin alfa is based on these clinical studies. Current adverse drug reactions reported in efavaleukin alfa clinical studies are erythema and pruritus, hypersensitivity, and RA. Potential risks are described in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to evaluate the PK of AMG 592 after single 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.

CCI [redacted]

CCI [redacted]

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints of the study are:

- C_{max}
- t_{max}
- AUC from time zero to time of last quantifiable concentration (AUC_{last})
- AUC_{inf}.

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

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

CCI [redacted]

CCI [redacted]

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

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 [redacted] subjects in each of the following 4 groups:

- Group 1: Chinese subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted]) SC injection
- Group 2: Chinese subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted]) SC injection
- Group 3: Japanese subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted]) SC injection
- Group 4: Caucasian subjects (n=[redacted]) will receive [redacted] AMG 592 given as one[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.

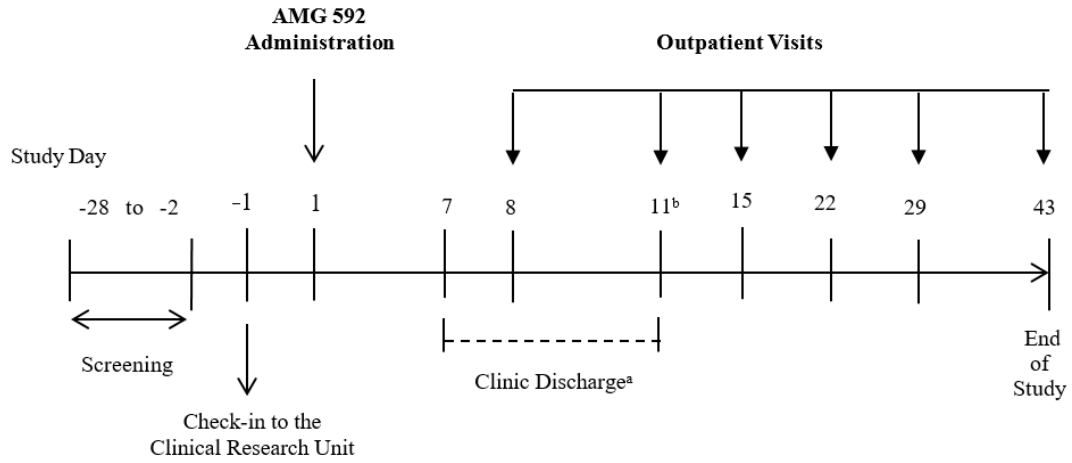
For subjects to be enrolled under Amendment 2, after discharge from the CRU on Day 7, subjects will return for outpatient visits on Days 8, 11, 15, 22, 29, and the end of study (EOS) visit on Day 43. (For subjects enrolled prior to Amendment 2 and discharged on Day 3, outpatient visits also included 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. A Schedule of Assessments is presented in Appendix 8.

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.

3.2. Discussion of Study Design

This study is an open-label investigation because the study endpoints are not believed to be subject to bias.

This study will not be randomized as all subjects within a group will receive the same study treatment, and because of the need to conduct the Chinese groups in sequential order. Because of the sequential nature, Chinese subjects cannot be randomized to dose level as the timing for each group will differ and may affect subject availability.

Subcutaneous injection was chosen because this is the intended clinical route of administration.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

3.3. Selection of Doses in the Study

AMG 592 doses were selected based on safety, PK, and PD results from the completed FIH study (20140324), PK study in Japanese healthy subjects (20180132), multiple-dose study in RA patients, ongoing multiple SC dose Phase 1b studies in patients with chronic GvHD and patients with SLE, as well as results from GLP toxicology studies in cynomolgus monkeys. The high dose of CCI [redacted] was chosen to evaluate the PK/PD response and because it is within the anticipated upper range of doses that will be used in Phase 2 and 3 studies. Results from Studies 20140324 and 20180132 as well as preliminary Phase 1b data indicate that AMG 592 is well

tolerated at doses up to CCI with acceptable safety and Treg selectivity. Exposures in the present study are anticipated to be lower than those at the NOAEL (exposure multiples of at least 16.3 and 3 for AUC and C_{max}, respectively) in the 6-month repeat-dose GLP toxicology study in the cynomolgus monkey (Study 122293).

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria prior to enrollment, unless otherwise stated:

1. Subject has provided informed consent before initiation of any study-specific activities/procedures.
2. Healthy male or female subjects, between 18 and 55 years of age (inclusive) at the time of Screening.
3. Chinese, Japanese, or Caucasian subject:
    - Chinese subjects must be of Chinese ancestry (4 grandparents and biological parents).
    - Japanese subjects must be first- or second-generation Japanese (4 grandparents and biological parents; subject or both of their parents must have been born in Japan).
    - Caucasian subjects are those who self-identify exclusively as such on the electronic case report form (eCRF) and also identify their biological parents as such.
4. In good health, determined by no clinically significant findings from medical history, PE, 12-lead electrocardiogram (ECG), vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).
5. Body mass index between 17 and 30 kg/m^2 (inclusive) at the time of Screening.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria prior to enrollment unless otherwise stated:

1. History or evidence, at Screening or Check-in, of a clinically significant disorder, condition, or disease not otherwise excluded that, in the opinion of the Investigator (or designee), would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
2. Evidence of scars, tattoos, or other skin lesions that may interfere with the injection site or injection site assessments.
3. History or evidence of clinically significant arrhythmia at Screening, including any clinically significant findings on the ECG taken at Check-in.

4. A QT interval corrected for heart rate using Fridericia's method (QTcF) interval > 450 msec in male subjects or > 470 msec in female subjects or history/evidence of long QT syndrome, at Screening or Check-in.
5. PR interval > 210 msec, at Screening or Check-in.
6. Second- or third-degree atrioventricular (AV) block, at Screening or Check-in.
7. Systolic blood pressure (BP) > 140 mmHg or < 90 mmHg, or diastolic BP > 90 mmHg, or HR > 100 bpm, at Screening or Check-in.
8. History of hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee) and in consultation with the Sponsor.
9. Poor peripheral venous access.
10. Estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation, at Screening.
11. Underlying condition that predisposes the subject to infections (eg, history of splenectomy).
12. HbA1C ≥ 7%, at Screening or Check-in.
13. Active tuberculosis (TB) requiring treatment or documented latent TB within the previous 3 years. All subjects will be required to have a QuantiFERON-TB Gold test performed at Screening. Also excluded are participants with evidence of a past TB infection without documented adequate therapy. Participants with a positive QuantiFERON-TB Gold test at Screening will not be eligible for the study. A QuantiFERON-TB Gold test performed within 4 weeks of dosing on Day 1 is acceptable as long as there is documentation of a negative result.
14. Subjects who have received live vaccines within 5 weeks prior to Screening, or plan to receive live vaccines within 105 days after administration of an investigational product.
15. Subjects who have received Coronavirus Disease 2019 (COVID-19) vaccine within 28 days prior to dosing, or plan to receive a COVID-19 vaccine within 28 days postdose; from 29 days postdose through EOS, vaccination for COVID-19 may be deemed acceptable for a subject following discussion and agreement between the Sponsor and the Investigator.
16. History of active infections (viral, bacterial, or fungal) within 21 days of receiving the investigational product.
17. Positive hepatitis B or hepatitis C panel (ie, positive hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody) at Screening, or a medical history for hepatitis B or C; and/or positive human immunodeficiency virus test, at Screening. Subjects whose results are compatible with prior vaccination may be included. Subjects with a history of hepatitis B vaccination without a history of hepatitis B or C are allowed to participate.
18. Use of any over-the-counter or prescription medications within 30 days or 5 half-lives (whichever is longer) of Check-in. Continued use, if applicable, will be reviewed by the Investigator (or designee) and in consultation with the Sponsor. Written documentation of this review and Sponsor acknowledgment is required for subject participation. Exceptions are listed below.

- Acetaminophen [paracetamol] up to 2 g per day for analgesia will be allowed.
- Hormonal contraception listed in Appendix 4 will be allowed.
- Hormone replacement therapy (eg, estrogen) will be allowed.

19. Use of any herbal medicines, vitamins, or supplements consumed within the 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.
20. Consumption of foods and beverages containing poppy seeds within 7 days prior to Check-in.
21. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
22. Alcohol consumption from 48 hours prior to Check-in.
23. Regular alcohol consumption of > 14 units per week for males and > 7 units for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
24. Use of tobacco- or nicotine-containing products within 6 months prior to Check-in.
25. Positive test for illicit drugs, cotinine (tobacco or nicotine use), and/or alcohol use at Screening or Check-in.
26. Consumption of caffeine-containing foods and beverages within 24 hours prior to Check-in.
27. Female subjects with a positive pregnancy test at Screening or Check-in.
28. Female subjects who are lactating/breastfeeding or who plan to breastfeed during the study through 90 days after the EOS visit.
29. Subjects who are unwilling to adhere to contraceptive requirements through 90 days after the EOS visit (see Appendix 4).
30. Subjects who are unwilling to abstain from sperm donation and ovum donation from Check-in until 90 days after the EOS visit (see Appendix 4).
31. Male subject with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
32. Male subject with a pregnant partner or partner planning to become pregnant while the subject is on study through 90 days after the EOS visit.
33. Subject has received a dose of an investigational drug within the past 90 days or 5 half-lives of the drug, whichever is longer, prior to Check-in.
34. Subjects who have previously completed or withdrawn from this study or any other study investigating AMG 592 or have previously received the investigational product.
35. Donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, or platelets from 6 weeks prior to Check-in.
36. Subjects who are unwilling to abide with study restrictions.
37. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

38. Subjects with abnormal laboratory results for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (ie, > upper limit of normal) and total bilirubin (ie, > upper limit of normal) at Screening and Checkin.

4.3. Screen Failures and Rescreening

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study because they do not meet eligibility requirements. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Subjects who have a screening laboratory test result that is out of range may have the test repeated once, and the subject may be enrolled if the repeated value is within range. This can be applied to any or all of the laboratory tests included in the exclusion criteria, and it can be disallowed for any critical tests at the discretion of the Investigator or Sponsor.

4.4. Subject Number and Identification

Subjects will have a unique identification number used at Screening. CCI [redacted]

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.5. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's eCRF, and efforts will be made to perform all EOS assessments, if possible (Appendix 8). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is residing at the CRU, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for additional follow-up visit(s). All withdrawn subjects will be

followed until resolution of all their adverse events or until the unresolved adverse events are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of adverse events thought to be related to the study drug will generally not be replaced.

4.6. Study Termination

The Sponsor may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice. Both the Sponsor and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The Investigator is to notify the Ethics Committee (EC) in writing of the study's completion or early termination and send a copy of the notification to the Sponsor. The Sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply investigational product and by what mechanism, after termination of the study.

In addition, the study may be terminated by the Sponsor at any time and for any reason. If the Sponsor decides to terminate the study, they will inform the Investigator as soon as possible.

5. STUDY TREATMENTS

Study treatment is defined as any investigational product, non-investigational product, placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as IMP and non-IMP, respectively.

5.1. Investigational Product

The IMP will be supplied by the Sponsor. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of the IMP shown in Table 1.

All supplies of investigational product, both bulk and subject-specific, will be stored in accordance with the manufacturer's instructions or pharmacy instructions. Until dispensed to the subjects, the IMP will be stored at the study site in a location that is locked with restricted access.

The IMP (solution containing[redacted] AMG 592) will be supplied by the Sponsor (or designee), along with the lot numbers and Certificates of Analysis. The IMP will be stored according to the instructions on the label.

Table 1: Investigational Product

	Investigational Medicinal Product:
Study Treatment Name	AMG 592
Unit Strength and Formulation	CCI [redacted]
Dosage Level	CCI [redacted]
Route of Administration	Subcutaneous injection
Accountability	The quantity administered, date administered, and lot number of the investigational medicinal product are to be recorded on each subject's electronic case report form.
Dosing Instructions	Treatment will be administered after the completion of all predose procedures.

5.2. Investigational Product Administration

Each SC injection will be administered by qualified and appropriately trained clinical staff to the lower abdomen. There are no posture requirements for dosing.

5.3. Treatment of Overdose

Neither the effects of overdose of AMG 592 nor an antidote to overdose are known.

5.3.1. Medical Devices

No investigational medical device will be used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care. Non-investigational medical devices (eg, syringes, sterile needles) that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

5.3.2. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either the Sponsor or by distributors and partners for whom the Sponsor manufactures the material. This includes any investigational product (AMG 592) provisioned and/or repackaged/modified by the Sponsor.

Any product complaint(s) associated with an investigational product (AMG 592) supplied by the Sponsor are to be reported according to the instructions provided in the Amgen IPIM.

5.4. Randomization

This study will not be randomized.

5.5. Blinding

This is an open-label study.

5.6. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- At each dosing occasion, a predose and postdose inventory of AMG 592 will be performed.

5.7. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of AMG 592 received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused AMG 592 will be returned to the Sponsor, retained at the study site, or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the EOS visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Acetaminophen (paracetamol) (2 g/day), hormone replacement therapy or oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an adverse event. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

Subjects will be required to fast from food overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations. Water may be consumed ad libitum throughout the study.

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

Foods and beverages containing poppy seeds will not be allowed from 7 days prior to Check-in until after the EOS visit.

Caffeine-containing foods and beverages will not be allowed from 24 hours prior to each clinic visit and while at the CRU.

Consumption of alcohol will not be permitted from 48 hours prior to each clinic visit. Alcohol intake will be limited to a maximum of 1 unit/day on all other days, while not in the CRU, from Screening through the EOS visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 6 months prior to Check-in until after the EOS visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before Check-in until after the EOS visit. Subjects will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, and platelets from 6 weeks prior to Check-in until 3 months after the EOS visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- PK blood samples
- safety assessments (ECGs will be scheduled before vital signs measurements)
- any other procedures.

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, safety laboratory assessments, and assessment of adverse events and serious adverse events.

Any blood sample collected according to the Schedule of Assessments (Appendix 8) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 8. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Serum concentrations of AMG 592 will be determined using validated analytical procedures. Specifics of the analytical method will be provided in a separate document.

CCI [redacted]

7.3. Anti-AMG 592 and Anti-IL-2 Assessments

Blood samples for antibody testing are to be collected at the times listed in the Schedule of Assessments (Appendix 8). Samples testing positive for anti-AMG 592 and/or anti-IL-2 antibodies will also be tested for neutralizing antibodies and may be further characterized. More frequent testing or testing for a longer period of time may be required in the event of a safety-related concern.

Subjects who test positive at the EOS timepoint for neutralizing antibodies to IL-2 or binding antibodies with potentially antibody-mediated clinical sequelae will be asked to return for follow-up testing. This testing is to occur approximately every 3 months starting from the EOS visit and continue until: 1) antibodies are no longer detectable or 2) the subject has been followed for a period of at least 12 months (± 4 weeks) post administration of AMG 592 (whichever is shorter). All follow-up results, both positive and negative, will be communicated to the study site.

7.4. Biomarker Development

7.4.1. Blood Samples for Biomarker Development

Blood samples for biomarker development will be collected at the times indicated in the Schedule of Assessments in Appendix 8. Procedures for collection, processing, and shipping of biomarker development samples will be detailed in a separate document.

7.4.2. Analytical Methodology

Blood samples for biomarker development may be used to explore possible relationships between exposure to AMG 592 and physiological responses in individual subjects or in the general population, as part of the overall development program for AMG 592. Specifics of the analytical methods will be provided in a separate document.

7.5. Safety and Tolerability Assessments

7.5.1. Adverse Events and Serious Adverse Events: Time Period and Frequency for Collecting and Reporting Safety Event Information

Adverse event definitions, assignment of severity and causality, and procedures for reporting serious adverse events are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to the EOS.

If an event is reported as beginning prior to signing of the ICF or occurs prior to initiation of study treatment on Day 1 and is assessed as not related to study procedures by the Investigator (or designee), the event will be recorded as subject medical history. Any events prior to study drug administration but deemed by the Investigator to be related to study procedures will be reported as adverse events. Any events occurring after study drug administration on Day 1 through the EOS visit will be reported as adverse events.

Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report adverse events occurring at any other time during the study.

Adverse Events

The adverse event grading scale to be used in this study is described in Appendix 1.

The Investigator is responsible for ensuring that all adverse events observed by the Investigator or reported by the subject (whether reported by the subject voluntarily or upon questioning, or noted on PE) from enrollment through the EOS visit are recorded/reported using the appropriate eCRF.

Serious Adverse Events

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of the ICF through 30 days after the last dose of study treatment or the EOS visit (whichever is later) are reported using the appropriate eCRF and reported on the paper-based Serious Adverse Event Report Form (described in Appendix 1).

All serious adverse events will be collected, recorded, and reported to the Sponsor within 24 hours of the Investigator’s knowledge of the event. The Investigator will

submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, Investigators are required to report serious adverse events that they become aware of after the EOS visit. If serious adverse events are reported, the Investigator is to report them to the Sponsor within 24 hours following the Investigator's knowledge of the event using the paper-based Serious Adverse Event Report Form.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the Sponsor's safety database as clinical trial cases and handled accordingly based on relationship to the investigational product.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed, where possible, until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up. This will be completed at the Investigator's (or designee's) discretion.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the eCRF.

Regulatory Reporting Requirements for Serious Adverse Events

If the subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.

Prompt notification by the Investigator to the Sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, ECs, and Investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the Sponsor will file it along with the IB and will notify the EC, if appropriate according to local requirements.

Safety Monitoring Plan

Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.

Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and pregnancies in female partners of male subjects will be collected after the start of study treatment and until 90 days after the dosing.

If a pregnancy and/or lactation is reported, the Investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow up with the Investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 3). Refer to Appendix 4 for contraceptive requirements.

A pregnancy test should be performed (at the end of the period of relevant systemic exposure) after discontinuing protocol-required therapies.

Additional on-treatment pregnancy testing may be performed at the Investigator's discretion or as required per local laws and regulations.

Further details regarding pregnancy and lactation are provided in Appendix 5.

7.5.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 8. Clinical laboratory evaluations are listed in Appendix 2.

The Investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in CRF/eCRF. The Investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 8. For all female subjects, a pregnancy test and follicle-stimulating hormone screen for postmenopausal status will be performed at the times indicated in the Schedule of Assessments in Appendix 8.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.5.3. Vital Signs

Supine BP, supine heart rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 8. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be supine for at least 5 minutes before BP and heart rate measurements. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as possible, but prior to the blood draw.

7.5.4. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 8. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF >500 msec
- QTcF change from the baseline (predose) is >60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.5.5. Physical Examination

A full PE or symptom-directed PE will be performed at the timepoints specified in the Schedule of Assessments in Appendix 8. The PE will also include a neurological exam. The neurological examination should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

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.

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

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

8.2.2. Pharmacodynamic Population

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

8.2.3. 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.

8.3. Pharmacokinetic Analyses

The serum PK parameters of AMG 592 will be calculated using standard noncompartmental methods.

The primary PK parameters are C_{max}, t_{max}, AUC_{last}, and AUC_{inf} for AMG 592. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis.

Additional PK parameters may be calculated. Specific details will be presented in the Statistical Analysis Plan for this study.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.5. Anti-AMG 592 and Anti-IL-2 Analyses

The formation of anti-AMG 592 and anti-IL-2 antibodies will be summarized descriptively. The incidence and percentage of subjects who develop antidrug antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

8.6. Safety Analysis

The number and percentage of subjects reporting any adverse events will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

No imputation will be done for safety assessments, and endpoints for clinical laboratory tests and vital signs will be summarized.

8.7. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

1. Amgen, Inc. Efavaleukin Alfa (AMG 592; Inflammatory Diseases) – Investigator's Brochure. (Version 5.0). 17 December 2020.

2. Yu A, Snowhite I, Vendrame F, et al. Selective IL-2 responsiveness of regulatory T cells through multiple intrinsic mechanisms support the use of low-dose IL-2 therapy in Type-1 diabetes. *Diabetes*. Published online: 09 January 2015 (doi: 10.2337/db 14-1322).

3. Gavin MA, Rasmussen JP, Fontenot JD, et al. Foxp3-dependent programme of regulatory T cell differentiation. *Nature*. 2007;445:771-775.

4. Fontenot JD, Rasmussen JP, Gavin MA, Rudensky AY. A function to interleukin 2 in Foxp3-expressing regulatory T cells. *Nature Immunol*. 2005;6:1142-1151.

10. APPENDICES

Appendix 1: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device, or procedure. • Note: Treatment-emergent adverse event will be defined in the Statistical Analysis Plan.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect

Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant adverse event/serious adverse event information in the event electronic case report form (eCRF).
- The Investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to the investigational product(s) and/or study-mandated procedures, and
  - Action taken.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the appropriate eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor in lieu of completion of the appropriate eCRF page.

- If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The Investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will use the following definitions:

Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated, usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	Discomfort enough to cause interference with usual activity causing discomfort but poses no significant or permanent risk of harm to the subject. Usually alleviated with additional specific therapeutic intervention.
SEVERE[a]	Incapacitating with inability to work or interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

[a] An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between investigational product(s), protocol-required therapy and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the Investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.
    - If a subject dies during participation in the study, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper Serious Adverse Event Report Form
• Facsimile transmission of the Serious Adverse Event Report Form (see Figure 2) is the preferred method to transmit this information. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.

Figure 2: Sample Serious Adverse Event Report Form

AMGEN 20200102 LabCorp Study # 8448873 AMG 592	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

Amgen (Sponsor) UK Safety Fax Number: + 0800 028 4223
If FAX is unavailable, email form to the following address: svc-ags-in-gb@amgen.com

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex ❑F ❑M	Race	If applicable, provide End of Study date

3. SERIOUS ADVERSE EVENT - ***Information in this section must also be entered on the Serious Adverse Event Summary CRF***

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____ Month____ Year____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by IP or an Amgen device used to administer the IP? If yes see section 10 AMG592 No/Yes <Device> No/Yes <Device> No/Yes <Device> No/Yes <Device> No/Yes	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: **01** Fatal; **02** Immediately life- threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other medically important serious event

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ❑No ❑Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 592 ❑Blinded ✔Open Label							Lot #_____ ❑ Unknown Serial #_____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot #_____ ❑ Unknown Serial #_____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot #_____ ❑ Unknown Serial #_____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot #_____ ❑ Unknown Serial_____ ❑ Unknown

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AMGEN 20200102 LabCorp Study # 8448873 AMG 592	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	Site Number	Subject ID Number	

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN 20200102 LabCorp Study # 8448873 AMG 592	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	Site Number	Subject ID Number	

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*	Title	Date

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Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Bilirubin[a] Gamma-glutamyl transferase Glucose HbA1C Inorganic phosphate Potassium QuantiFERON-TB Gold test Sodium Total CO_2 (measured as bicarbonate) Total creatine kinase Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Serology[b]:	**Drug screen[c]:**	**Hormone panel - females only:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test Alcohol breath test	Follicle-stimulating hormone[b] Serum pregnancy test (human chorionic gonadotropin)[d] Urine pregnancy test[d]
		Other Tests:
		Hepatotoxicity only: International normalized ratio (INR)[e] Estimated glomerular filtration rate(eGFR)[f] Creatine kinase MB fraction[c]

[a] Includes total, direct, and indirect.
[b] Only analyzed at Screening.
[c] Only analyzed at Screening and Check-in.
[d] Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[e] International normalized ratio will be tested if hepatotoxicity is suspected, per guidelines presented in Appendix 7.
[f] Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease equation.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations	7.5	9	67.5
Serology	3.5	1	3.5
AMG 592 pharmacokinetics	3.5	15	52.5
Lymphocyte subsets	9	6	54
Biomarker development samples	5	8	40
Anti-AMG 592 and anti-IL-2 Antibodies	3.5	4	14
Total:			231.5

FSH = follicle-stimulating hormone; IL-2 = interleukin 2

If additional blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: Contraception Requirements

All subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they conceive a child during treatment and for 90 days after the end of study (EOS) visit.

Additional medications given during the study may alter the contraceptive requirements. The Investigator must discuss these contraceptive changes with the subject.

Definitions

Women of Childbearing Potential:

Premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Non-Childbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Requirements

Female Subjects

Female subjects who are of non-childbearing potential will not be required to use contraception.

Female subjects of childbearing potential must be willing to use 2 methods [1 primary (highly effective) and 1 secondary method] of birth control from the time of signing the informed consent form until 90 days after the EOS visit.

Primary (highly effective) methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill associated with inhibition of ovulation (as prescribed) without supplementary iron (ie, Loestrin Fe, Junel Fe, and Lo Loestrin Fe are prohibited)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
    - Bilateral tubal ligation with confirmation of surgical success
    - Regulatory approved method of hysteroscopic bilateral tubal occlusion with confirmation of occlusion of the fallopian tubes
- hormonal implant
- hormonal or non-hormonal intrauterine device (IUD or IUS)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects should refrain from donation of ova from Check-in (Day -1) until 90 days after the EOS visit.

Male Subjects:

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception by female partner from Check-in until 90 days after the EOS visit. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or regulatory approved method of hysteroscopic bilateral tubal occlusion)
- hormonal implant
- hormonal or non-hormonal IUD
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide.

Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the EOS visit.

Sexual Abstinence

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the informed consent form (ICF) until 90 days after the EOS visit.

Same-sex Relationships

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the EOS visit.

Appendix 5: Collection of Pregnancy and Lactation Information

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 90 days after EOS.
- Information will be recorded on the Pregnancy Notification Form (see Figure 3). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 90 days after EOS. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse events or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to the Sponsor as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly), the Investigator will report the event as a serious adverse event.

- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator will be reported to Amgen Global Patient Safety as described in Appendix 1. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 4.5 for details).

Male Subjects with Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 90 days after EOS, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 3) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The Investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- The Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 90 days after the EOS.

- Information will be recorded on the Lactation Notification Form (Figure 4) and submitted to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event.
- Study treatment will be discontinued if the female subject breastfeeds during the study.

With the female subject's signed authorization for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 90 days after discontinuing protocol-required therapies.

Figure 3: Pregnancy Notification Form

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20200102 LabCorp # 8448873_____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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Figure 4: Lactation Notification Form

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20200102 LabCorp # 8448873_____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐Yes ☐No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
- Notifying the EC of serious adverse events or other significant safety findings as required by EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

An initial sample ICF will be provided for the Investigator (or designee) to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Study Manager to the Investigator. The written ICF is to be prepared in the language(s) of the potential study participant population.

The Investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and the Ethics Committee (EC) or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 21 days from the previous ICF signature date.

Subject Data Protection

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to the Sponsor.

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic case report form (eCRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to the Sponsor, subjects are to be identified by their unique subject identification number, (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to the Sponsor (eg, signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the EC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential information of the Sponsor, Amgen Inc. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written permission from the Sponsor.

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic CRF (eCRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the Investigator, except as described below.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- The contract research organization (CRO) is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify

the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

The policy for publication of data obtained during this study will be documented in the clinical study agreement.

Appendix 7: Hepatotoxicity: Suggested Actions and Follow-up Assessments

Subjects with normal hepatic function at Screening who experience aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3 x upper limit of normal (ULN) or subjects with elevated values before drug exposure who have a 2-fold increase above baseline values (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009) are to undergo clinical assessments and a period of "close observation" until abnormalities return to normal or to the subject's baseline level as described below.

Clinical Assessments and Observation

Assessments that are to be performed during this period include:

- Repeat AST, ALT, alkaline phosphatase, bilirubin (total and direct), and international normalized ratio (INR) within 24 hours
- In cases of total bilirubin (TBL) > 2 x ULN or INR > 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever

    - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
    - Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or are considered stable by the Investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential drug-induced liver injury (DILI) event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding electronic case report form (eCRF).

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms

- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis).

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, ie, cases of AST or ALT > 3 x ULN and concurrent TBL > 2 x ULN or INR > 1.5 (for subjects not on anticoagulation therapy) without evidence of alternative cause of the elevations, require the following:

- The event is to be reported to the Sponsor as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate eCRF captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Sponsor.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 1.

Appendix 8: Schedule of Assessments

PROCEDURE	Screening	Check-in			Treatment Period														
		Resident at the Clinical Research Unit																	
Study Day	**-28 to -2**	**-1**	**1**	**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**29**	**43[a] (EOS)/ET**
Relative to Dosing (Hours)			**Pre**	**0**	**6**	**12**	**16**	**24**	**48**	**72**	**96**	**120**	**144**	**168**	**240**	**336**	**504**	**672**	**1008**
GENERAL AND SAFETY ASSESSMENTS																			
Informed Consent	X																		
In-house Residency[b]		◄	—	—	—	—	—	—	—	—	—	—	►	◄	►				
Physical Examination[c]	X	X							X				X		X		X	X	X
Medical History	X	X[d]																	
Weight	X																		
Height	X																		
ECG[e]	X	X																	
Vital Signs[f]	X	X	X					X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[g]	◄	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	►
Serious Adverse Events[h]	X	◄	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	►
Concomitant Therapy Review[i]	◄	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	►
LABORATORY ASSESSMENTS																			
Pregnancy Test[j]	X	X																	X
Chemistry and Hematology[k]	X	X						X	X		X		X		X		X		X
Serology	X																		
Urinary Drug Screen	X	X																	
Alcohol Breath Test	X	X																	
Urinalysis	X	X							X				X[k]		X		X		X
eGFR[l]	X																		
FSH[m]	X																		
BIOMARKER AND IMMUNOLOGICAL ASSESSMENTS																			
Lymphocyte Subsets		X						X						X		X	X		X
Biomarker Development Samples		X			X	X			X[o]					X		X	X		X
Anti-AMG 592 and Anti-IL-2 Antibodies		X														X		X	X
PHARMACOKINETIC ASSESSMENTS																			
AMG 592 Serum PK Collection[n]			X		X	X	X	X	X	X	X	X		X	X	X	X	X	X
STUDY TREATMENT																			
AMG 592 Administration				X															

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = follicle-stimulating hormone; PE = physical examination; PK = pharmacokinetic

[a] Subjects who test positive at the EOS timepoint for neutralizing antibodies to IL-2 or binding antibodies with potentially antibody-mediated clinical sequelae that are considered potentially related to an anti-AMG 592 antibody response will be asked to return for additional follow-up testing every 3 months until antibodies are no longer detectable or up to 12 months' post administration of AMG 592 (whichever is shorter).

[b] Inhouse residency from Day 1 through the completion of all assessments on Day 7. Solid line indicates time that subjects are required to stay in the CRU. Dashed line indicates that subjects may stay in the CRU after Day 7 until a maximum of Day 11 if they choose (to reduce travel and accommodation burden on subjects); alternatively, the Investigator may require subjects to remain in-house for 1 or more days after Day 7 (up to Day 11) at their discretion, based on other signs and symptoms requiring monitoring. Only subjects enrolled after Amendment 2 will have discharge study procedures completed on Day 7 at the earliest. (All other subjects enrolled prior to Amendment 2 had discharge study procedures completed by Day 3 at the earliest.) The latest discharge day for all subjects is Day 11.

[c] Physical examination to include a neurological examination. A full PE will be conducted at Screening and at discharge (Day 7 at the earliest). A symptom-directed PE will be conducted on Days -1, 3, 11, 22, 29, and 43/EOS. Only subjects enrolled after Amendment 2 will have discharge study procedures completed on Day 7 at the earliest. (All other subjects enrolled prior to Amendment 2 had discharge study procedures completed by Day 3 at the earliest.) The latest discharge day for all subjects is Day 11.

[d] Interim medical history only.

[e] Electrocardiogram (ECG) will be single 12-lead ECG, prior to blood draws or invasive procedures.

[f] Supine blood pressure (BP), supine heart rate, respiratory rate, and oral body temperature. Heart rate and BP will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes. For subjects enrolled after Amendment 2, additional days for vital signs measurements will include Days 4, 5, 7, 15, and 29.

[g] Adverse events will be recorded from initiation of study treatment on Day 1 until the EOS. Any events prior to study drug administration but deemed by the Investigator to be related to study procedures will be reported as adverse events.

[h] Serious adverse events will be recorded from the time the subject signs the informed consent form until the EOS.

[i] Prior and concomitant medication administration will be recorded beginning at informed consent. Also, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) before Day 1 for over-the-counter or prescription medications, and 30 days prior to Check-in for herbal medicines (eg, St. John's wort), vitamins, or supplements will be recorded on the subject's electronic case report form.

[j] Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

[k] Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations. Only subjects enrolled after Amendment 2 will have additional chemistry and hematology laboratory evaluations on Days 2, 5, and 7 and will have the additional urinalysis procedure at discharge (Day 7 at the earliest). (All other subjects enrolled prior to Amendment 2 had urinalysis conducted at discharge on Day 3 at the earliest.)

[l] The eGFR will be calculated using the Modification of Diet in Renal Disease equation.

[m] Performed in females only.

[n] Blood samples for determination of AMG 592 serum concentrations and PK parameters will be collected: Predose; 6, 12, and 16 hours postdose; and on Days 2 (24 hours postdose), 3, 4, 5, 6, 8, 11, 15, 22, 29, and 43 (EOS) following administration of AMG 592 on Day 1. The postdose samples collected on Days 1 and 2 (6, 12, 16, and 24 hour samples) will have a sampling window of ± 30 minutes, postdose samples collected on Days 3 and 4 will have a sampling window of ± 6 hours, postdose samples collected on Days 5 through Day 15 will have a sampling window of ± 1 day, postdose samples taken on Days 22 and 29 will have a sampling window of ± 2 days, and postdose samples taken on Day 43 (EOS) will have a sampling window of ± 4 days. Times of all PK samples will be recorded to the nearest minute.

[o] Only subjects enrolled after Amendment 2 will have additional biomarker development sample assessment on Day 3.

Approval Signatures

Document Name:	Protocol Amendment efavaleukin alfa 20200102 2
Document Description:	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
Document Number:	CLIN-000265267
Approval Date:	29 Apr 2022
Type of Study Protocol:	Amendment
Protocol Amendment No.:	2

Document Approvals	
Reason for Signing: Management	Name: PPD Date of Signature: 28-Apr-2022 19:32:03 GMT+0000
Reason for Signing: Functional Area	Name: PPD Date of Signature: 29-Apr-2022 15:12:07 GMT+0000

Protocol

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

Protocol Status: Final

Protocol Amendment 1
Protocol Amendment 1 Date: 08 December 2021
Original Protocol Version 1.0 Date: 01 April 2021

Investigational Product: AMG 592 (efavaleukin alfa)

Amgen Protocol Reference Number: 20200102
Labcorp Drug Development Study Number: 8448873
IND Number: 131270

Sponsor:
Amgen Inc.
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INVESTIGATOR AGREEMENT

I have read the protocol entitled "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," and agree to conduct the study as described herein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____

Signature

_____ _____

PPD Date (DD Month YYYY)

STUDY IDENTIFICATION

Sponsor	Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320
Sponsor's Study Contact	PPD
Medical Monitor	PPD
Sponsor's Study Manager	PPD
Labcorp Drug Development Program Manager	PPD
Statistician	PPD

SYNOPSIS

Title of study: 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

Objectives:

The primary objective of the study is:

- to evaluate the pharmacokinetics (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-interleukin (IL)2 antibodies in healthy Chinese, Japanese, and Caucasian subjects after single SC administration of AMG 592.

CCI [redacted]

Study design:

This will be an open-label, single-dose, sequential-group study in 2 groups of healthy Chinese subjects and 1 group of Japanese subjects. In addition, a group of Caucasian subjects will be evaluated at the high dose for comparison. Potential subjects will be screened within 28 days prior to the dose. Subjects will be admitted into the clinical research unit (CRU) on Day -1 and will be confined to the CRU until discharge on Day 3 (individual subjects may be required to stay longer than Day 3 [to a maximum of Day 11] at the request of the Investigator based on emergence and progression of adverse events or other signs and symptoms requiring monitoring). The clinical conduct for the 2 groups of Chinese subjects will be done in a sequential manner, such that Group 1 will be enrolled and dosed first, with a postdose safety evaluation period of at least 14 days prior to initiation of dosing in Group 2. Chinese subjects (n = [redacted]/group) will receive a single SC dose of AMG 592 at CCI [redacted] (Group 1) or CCI [redacted] (Group 2). Japanese subjects (n = [redacted]) will receive a single SC dose of AMG 592 at CCI [redacted] (Group 3). Caucasian subjects (n = [redacted]) will receive a single SC dose of AMG 592 at CCI [redacted] (Group 4). After discharge from the research facility, subjects will return to the CRU for outpatient visits on Days 4, 5, 6, 8, 11, 15, 22, 29, and at the end of study (EOS) visit on Day 43. A subject's participation in the study will conclude at the completion of the EOS visit; however, subjects who test positive at the EOS timepoint for neutralizing antibodies to IL2 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 from dosing (whichever is shorter).

Number of subjects:

Approximately 32 subjects ([redacted] per group) will be enrolled in this study.

Diagnosis and main criteria for inclusion:

Healthy male or female subjects of Chinese ancestry, first- or second-generation Japanese subjects, and Caucasian subjects, 18 to 55 years of age (inclusive), body mass index of 17 to 30 kg/m^2 (inclusive).

Investigational products, dose, and mode of administration:

Investigational Medicinal Product: CCI [redacted] AMG 592 given as a CCI [redacted] SC injection, CCI [redacted] AMG 592 given as a CCI [redacted] SC injection.

Group 1 = CCI [redacted] SC
Group 2 = CCI [redacted] SC
Group 3 = CCI [redacted] SC
Group 4 = CCI [redacted] SC

Duration of subject participation in the study:

Planned Screening duration: approximately 4 weeks.
Planned study duration (Screening to EOS): approximately 10 weeks.

Primary endpoints:
The primary endpoints for this study are PK parameters: maximum observed serum concentration (C_{max}), the time of maximum observed serum concentration (t_{max}), area under the serum concentration-time curve (AUC) from time zero to time of last quantifiable concentration (AUC_{last}), and AUC from time zero to infinity (AUC_{inf}).
Secondary endpoints:
Secondary endpoints for this study are: treatment-emergent adverse events and serious adverse events (including clinically significant changes in physical examinations), clinical laboratory tests, vital signs, and anti-AMG 592 and anti-IL-2 antibody formation.
CCI [redacted]

Statistical methods:
Data will be analyzed for all subjects who were enrolled and received a dose of AMG 592. Descriptive statistics by treatment arm will be provided for selected demographics, safety, PK parameters, and PD and immunogenicity data. Descriptive statistics on continuous measurements will include geometric and arithmetic means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. The PK, vital signs, and clinical laboratory data will be summarized for each timepoint when samples are collected.
The final safety analysis for the study will be performed at the end of the study. Adverse events will be summarized using descriptive methodology. Each adverse event will be coded using the Medical Dictionary for Regulatory Activities. No imputation will be done for safety assessments, and endpoints for clinical laboratory tests and vital signs will be summarized. No inferential statistical analysis is planned.
Additional details will be included in the Statistical Analysis Plan.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC_{inf}	area under the serum concentration-time curve from time zero to infinity
AUC_{last}	area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AV	atrioventricular
BP	blood pressure
CD4	cluster of differentiation 4
CD25	alpha chain of the interleukin 2 receptor
CFR	Code of Federal Regulations
C_{max}	maximum observed serum concentration
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CRU	clinical research unit
DILI	drug-induced liver injury
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
FIH	first-in-human
FOXP3	forkhead box P3; an essential transcription factor of Treg function, upregulated by IL-2R signals
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GvHD	graft-versus-host disease
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IL	interleukin
IL-2R	interleukin 2 receptor
IL-2RA	interleukin 2 receptor alpha chain
IL-2RB	interleukin 2 receptor beta chain
ILC2	innate lymphoid cells
IMP	investigational medicinal product
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	institutional review board

IUD	intrauterine device
NK	natural killer
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic
PE	physical examination
PK	pharmacokinetic(s)
Q2W	every 2 weeks
QTcF	QT interval corrected for heart rate using Fridericia's method
QW	once weekly
RA	rheumatoid arthritis
SC	subcutaneous
SLE	systemic lupus erythematosus
$t_{1/2}$	terminal elimination half-life
TB	tuberculosis
TBL	total bilirubin
Tcon	conventional T cells
t_{max}	time of the maximum observed serum concentration
Tregs	regulatory T cells
ULN	upper limit of normal

1. INTRODUCTION

Refer to the Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational medicinal product (IMP).

1.1. Background

Investigational Medicinal Product

Regulatory T cells (Tregs) are a subset of cluster of differentiation 4 (CD4) T cells that suppress inflammation and whose numbers and function are maintained by interleukin (IL)-2. In addition to Treg, IL-2-responsive lymphocytes include conventional CD4 and CD8 T (Tcon) cells, natural killer (NK) cells, and innate lymphoid cells (ILC2). A loss in the homeostatic balance between Tregs and other lymphocytes is considered a causative factor in many inflammatory conditions.

AMG 592 (efavaleukin alfa) is an Fc-IL-2 mutein that contains 2 mutations in the IL-2 domain. To increase the Treg selectivity of IL-2, 1 mutation is in the region that binds the beta chain of the IL-2 receptor (IL-2RB). This mutation reduces its signaling potency and increases its dependence on expression of interleukin 2 receptor alpha chain (IL-2RA/CD25). It drives a positive feedback loop enforcing Treg phenotype, abundance, and IL-2 responsiveness over effects on other lymphocytes. The other mutation is in an internal region of IL-2 and improves manufacturability of AMG 592 but does not alter its biological activity.[2,3,4]

The IL-2R is composed of 3 chains: IL-2RB and IL-2R gamma, which together deliver the intracellular IL-2R signal, and IL-2RA (CD25), which stabilizes IL-2 association with IL-2RBG but does not contain a signaling domain. The alpha chain of the IL-2 receptor (CD25) is highly expressed on Treg, and IL-2R signaling in Treg promotes expression of both CD25 and FOXP3, the essential transcription factor for Treg development and function. High FOXP3 expression promotes both full Treg suppressor activity and high CD25 expression, resulting in a positive feedback loop enforcing Treg phenotype, abundance, and IL-2 responsiveness.[2,3,4]

The mutation in the IL-2RB-binding region of IL-2 results in increased dependence on CD25 for IL-2R signaling compared with wild-type IL-2. Thus, efavaleukin alfa preferentially drives this positive feedback loop in Treg over effects on other lymphocytes (ie, other T cells and ILC2 which may express CD25 but do not express FOXP3, and NK cells which express little or no CD25 and no FOXP3). Compared with aldesleukin, efavaleukin alfa exhibits greatly improved selectivity for Treg over Tcon and NK cells both in vitro and in vivo, potentially resulting in an improved therapeutic margin. In addition, the Fc domain of AMG 592 confers a prolonged half-life compared with aldesleukin, thus reducing the dosing frequency required to maintain Treg enrichment

Nonclinical in vitro and in vivo studies have demonstrated that AMG 592 exhibits greater selectivity for inducing Treg expansion over the expansion of CD4 and CD8 T cells, and NK cells, relative to low dose, recombinant IL-2. This greater selectivity of AMG 592 has promise for greater efficacy and a wider therapeutic margin in inflammatory diseases relative to low-dose recombinant IL-2-based modalities.

Amgen is developing AMG 592 as a treatment for multiple inflammatory diseases including systemic lupus erythematosus (SLE), steroid-refractory chronic graft-versus-host disease (GvHD), and ulcerative colitis. This study is designed to evaluate whether pharmacokinetic (PK) and safety data in Chinese and Japanese subjects are similar to those from the global population.

A summary of completed and ongoing clinical studies for AMG 592 is provided in the IB.[1]

Changes to Study Protocol 20200102

The current study (20200102) was placed on a temporary hold during recruitment of the Japanese CCI cohort due to the occurrence of delayed-onset AEs in the majority of subjects administered AMG 592 thus far in the study. The intention of the hold was to prepare a protocol amendment which would allow for the PI to direct that subjects should remain in the CRU beyond Day 3 for longer observation for delayed-onset AEs. As of 27Sept2021, CCI subjects in the Caucasian cohort and CCI subjects in the Japanese cohort had been enrolled, dosed, and completed all scheduled study procedures. The remaining CCI Japanese subjects and all Chinese subjects will be enrolled under the amended protocol (Protocol Amendment 1).

1.2. Pharmacokinetics

In a first-in-human (FIH) study (Study 20140324), PK results of AMG 592 in healthy subjects following single-dose subcutaneous (SC) administration of AMG 592 are available for doses of CCI. Results show dose-related increases in AMG 592 serum exposure (as assessed by maximum observed concentration [C_{max}] and area under the serum concentration-time curve [AUC] from time zero to infinity [AUC_{inf}]) with approximately dose-proportional increase over the CCI. Following SC administration, the median time to maximum observed serum concentration (t_{max}) ranged from approximately 0.5 to 1 day with terminal phase half-life ($t_{1/2}$) about 11 to 13 hours postdose at doses CCI.

In a single-dose PK study in healthy Japanese subjects (Study 20180132), exposure of AMG 592, assessed by C_{max} and AUC_{inf}, increased approximately dose proportionally over the CCI. Mean C_{max} and AUC_{inf} exhibited CCI. The median t_{max} was 14 hours in the AMG 592 CCI cohort and 24 hours in the AMG 592 CCI cohort. For the CCI cohort, the mean half-life, apparent drug clearance, volume of distribution, and mean residence time was 11.7 hours, 1.29 L/hour, 21.9 L, and 33.2 hours, respectively. For the CCI cohort, the mean half-life, apparent drug clearance, volume of distribution, and mean residence time was 9.68 hours, 0.852 L/hour, 11.7 L, and 39.5 hours, respectively.

In a multiple-dose study in patients with active rheumatoid arthritis (RA), exposure to AMG 592, as expressed in AUC and C_{max}, increased with increasing dose from CCI every 2 weeks (Q2W) to CCI once weekly (QW) to CCI Q2W. Peak concentrations were observed about 6 to 12 hours following dosing, with half-lives that ranged from about 10 to 40 hours. Moderate drug accumulation was observed for CCI Q2W and CCI QW. There were not enough data to determine the accumulation ratio for the CCI Q2W dose.

1.3. Study Rationale

The highest dose of AMG 592 previously evaluated in healthy Japanese and Caucasian subjects is CCI, and a dose of CCI has demonstrated Treg selectivity and acceptable safety in subjects with SLE. As AMG 592 has not previously been studied in healthy Chinese subjects, CCI was chosen as the low-dose level to permit direct comparison with results from previous studies. Chinese, Japanese, and Caucasian subjects were selected in order to allow comparison to previous data and extrapolation to future studies, to look for possible ethnic variation in PK or PD parameters, and as part of the effort to ensure that proper dose regimens are recommended for the appropriate patient populations of different ethnicities. The current study should inform dose selection and design of future Phase 2 and 3 studies.

1.4. Benefit-risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study. Refer to the IB[1] for more information.

1.4.1. Therapeutic Context

1.4.1.1. Benefits

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study.

1.4.1.2. Risks

The safety of AMG 592 (efavaleukin alfa) has been studied in healthy volunteers and in SLE, chronic GvHD, and RA patients. Prior to the current study, approximately 136 subjects have been exposed to efavaleukin alfa in Amgen clinical studies. Single SC doses of up to CCI of efavaleukin alfa have been studied in healthy volunteers. Repeated SC doses of up to CCI of efavaleukin alfa administered Q2W have been studied in subjects with chronic GvHD over the course of a 52-week period. Doses up to CCI Q2W have been studied in subjects with SLE and up to CCI Q2W in subjects with RA over the course of a 12-week period. The safety profile of efavaleukin alfa is based on these clinical studies. Current adverse drug reactions reported in efavaleukin alfa clinical studies are erythema and pruritus, hypersensitivity, and RA. Potential risks are described in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to evaluate the PK of AMG 592 after single 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.

CCI [redacted]

[redacted]

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints of the study are:

- C_{max}
- t_{max}
- AUC from time zero to time of last quantifiable concentration (AUC_{last})
- AUC_{inf}.

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

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

CCI [redacted]

[redacted]

[redacted]

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

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 [redacted] subjects in each of the 4 groups.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to dose administration. Eligible subjects will be admitted into the clinical research unit (CRU) for Check-in on Day 1 and be confined to the CRU until clinic discharge on Day 3. Individual subjects may be required to remain in the CRU for safety observations beyond Day 3 (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. Japanese and Caucasian subjects will be assigned to Groups 3 and 4, respectively. Aside from the sequential conduct for Groups 1 and 2, there is no priority or required order for conduct of the different ethnic groups.

On Day 1, AMG 592 will be administered as a single SC injection.

- Group 1: Chinese subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted] SC injection
- Group 2: Chinese subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted] SC injection
- Group 3: Japanese subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted] SC injection
- Group 4: Caucasian subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted] SC injection

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

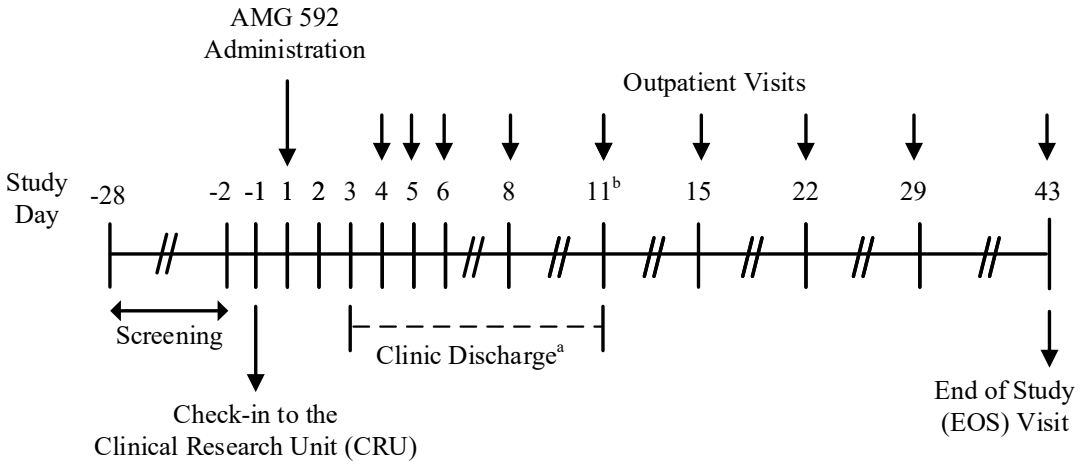
After discharge from the CRU, subjects will return for outpatient visits on Days 4, 5, 6, 8, 11, 15, 22, 29, and the end of study (EOS) visit on Day 43. It is anticipated that many subjects will be traveling a great distance to the CRU in order to participate in the study; therefore, to reduce unnecessary 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 3 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 3 (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 3, 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 3 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. A Schedule of Assessments is presented in Appendix 8.

Figure 1: Study Design



Note: Dashed line indicates that subjects may remain in the CRU beyond scheduled discharge on Day 3, 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 3. Subjects may reside at the CRU after discharge on Day 3 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 3 (to a maximum of Day 11) based on the emergence and progression of adverse events or clinical signs and symptoms of adverse drug reaction.

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 reactions.

3.2. Discussion of Study Design

This study is an open-label investigation because the study endpoints are not believed to be subject to bias.

This study will not be randomized as all subjects within a group will receive the same study treatment, and because of the need to conduct the Chinese groups in sequential order. Because of the sequential nature, Chinese subjects cannot be randomized to dose level as the timing for each group will differ and may affect subject availability.

Subcutaneous injection was chosen because this is the intended clinical route of administration.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

3.3. Selection of Doses in the Study

AMG 592 doses were selected based on safety, PK, and PD results from the completed FIH study (20140324), PK study in Japanese healthy subjects (20180132), multiple-dose study in RA patients, ongoing multiple SC dose Phase 1b studies in patients with chronic GvHD and patients with SLE, as well as results from GLP toxicology studies in cynomolgus monkeys. The high dose of CCI was chosen to evaluate the PK/PD response and because it is within the anticipated upper range of doses that will be used in Phase 2 and 3 studies. Results from Studies 20140324 and 20180132 as well as preliminary Phase 1b data indicate that AMG 592 is well tolerated at doses up to CCI with acceptable safety and Treg selectivity. Exposures in the present study are anticipated to be lower than those at the NOAEL (exposure multiples of at least 16.3 and 3 for AUC and C_{max}, respectively) in the 6-month repeat-dose GLP toxicology study in the cynomolgus monkey (Study 122293).

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria prior to enrollment, unless otherwise stated:

1. Subject has provided informed consent before initiation of any study-specific activities/procedures.
2. Healthy male or female subjects, between 18 and 55 years of age (inclusive) at the time of Screening.
3. Chinese, Japanese, or Caucasian subject:
    - Chinese subjects must be of Chinese ancestry (4 grandparents and biological parents).
    - Japanese subjects must be first- or second-generation Japanese (4 grandparents and biological parents; subject or both of their parents must have been born in Japan).
    - Caucasian subjects are those who self-identify exclusively as such on the electronic case report form (eCRF) and also identify their biological parents as such.
4. In good health, determined by no clinically significant findings from medical history, PE, 12-lead electrocardiogram (ECG), vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).
5. Body mass index between 17 and 30 kg/m^2 (inclusive) at the time of Screening.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria prior to enrollment unless otherwise stated:

1. History or evidence, at Screening or Check-in, of a clinically significant disorder, condition, or disease not otherwise excluded that, in the opinion of the Investigator (or designee), would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
2. Evidence of scars, tattoos, or other skin lesions that may interfere with the injection site or injection site assessments.
3. History or evidence of clinically significant arrhythmia at Screening, including any clinically significant findings on the ECG taken at Check-in.
4. A QT interval corrected for heart rate using Fridericia's method (QTcF) interval > 450 msec in male subjects or > 470 msec in female subjects or history/evidence of long QT syndrome, at Screening or Check-in.
5. PR interval > 210 msec, at Screening or Check-in.
6. Second- or third-degree atrioventricular (AV) block, at Screening or Check-in.
7. Systolic blood pressure (BP) > 140 mmHg or < 90 mmHg, or diastolic BP > 90 mmHg, or HR > 100 bpm, at Screening or Check-in.
8. History of hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee) and in consultation with the Sponsor.
9. Poor peripheral venous access.
10. Estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation, at Screening or Check-in.
11. Underlying condition that predisposes the subject to infections (eg, history of splenectomy).
12. HbA1C ≥ 7%, at Screening or Check-in.
13. Active tuberculosis (TB) requiring treatment or documented latent TB within the previous 3 years. All subjects will be required to have a QuantiFERON-TB Gold test performed at Screening. Also excluded are participants with evidence of a past TB infection without documented adequate therapy. Participants with a positive QuantiFERON-TB Gold test at Screening will not be eligible for the study. A QuantiFERON-TB Gold test performed within 4 weeks of dosing on Day 1 is acceptable as long as there is documentation of a negative result.
14. Subjects who have received live vaccines within 5 weeks prior to Screening, or plan to receive live vaccines within 105 days after administration of an investigational product.
15. Subjects who have received Coronavirus Disease 2019 (COVID-19) vaccine within 28 days prior to dosing, or plan to receive a COVID-19 vaccine within 28 days postdose; from 29 days postdose through EOS, vaccination for COVID-19 may be deemed acceptable for a subject following discussion and agreement between the sponsor and the investigator.
16. History of active infections (viral, bacterial, or fungal) within 21 days of receiving the investigational product.

17. Positive hepatitis B or hepatitis C panel and/or positive human immunodeficiency virus test, at Screening. Subjects whose results are compatible with prior vaccination may be included.
18. Use of any over-the-counter or prescription medications within 30 days or 5 half-lives (whichever is longer) of Check-in. Continued use, if applicable, will be reviewed by the Investigator (or designee) and in consultation with the Sponsor. Written documentation of this review and Sponsor acknowledgment is required for subject participation. Exceptions are listed below.
    - Acetaminophen [paracetamol] up to 2 g per day for analgesia will be allowed.
    - Hormonal contraception listed in Appendix 4 will be allowed.
    - Hormone replacement therapy (eg, estrogen) will be allowed.
19. Use of any herbal medicines, vitamins, or supplements consumed within the 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.
20. Consumption of foods and beverages containing poppy seeds within 7 days prior to Check-in.
21. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
22. Alcohol consumption from 48 hours prior to Check-in.
23. Regular alcohol consumption of > 14 units per week for males and > 7 units for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
24. Use of tobacco- or nicotine-containing products within 6 months prior to Check-in.
25. Positive test for illicit drugs, cotinine (tobacco or nicotine use), and/or alcohol use at Screening or Check-in.
26. Consumption of caffeine-containing foods and beverages within 24 hours prior to Check-in.
27. Female subjects with a positive pregnancy test at Screening or Check-in.
28. Female subjects who are lactating/breastfeeding or who plan to breastfeed during the study through 90 days after the EOS visit.
29. Subjects who are unwilling to adhere to contraceptive requirements through 90 days after the EOS visit (see Appendix 4).
30. Subjects who are unwilling to abstain from sperm donation and ovum donation from Check-in until 90 days after the EOS visit (see Appendix 4).
31. Male subject with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
32. Male subject with a pregnant partner or partner planning to become pregnant while the subject is on study through 90 days after the EOS visit.
33. Subject has received a dose of an investigational drug within the past 90 days or 5 half-lives of the drug, whichever is longer, prior to Check-in.

34. Subjects who have previously completed or withdrawn from this study or any other study investigating AMG 592 or have previously received the investigational product.
35. Donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, or platelets from 6 weeks prior to Check-in.
36. Subjects who are unwilling to abide with study restrictions.
37. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

4.3. Screen Failures and Rescreening

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study because they do not meet eligibility requirements. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Subjects who have a screening laboratory test result that is out of range may have the test repeated once, and the subject may be enrolled if the repeated value is within range. This can be applied to any or all of the laboratory tests included in the exclusion criteria, and it can be disallowed for any critical tests at the discretion of the Investigator or Sponsor.

4.4. Subject Number and Identification

Subjects will have a unique identification number used at Screening. CCI [redacted]

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.5. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's eCRF, and efforts will be made to perform all EOS assessments, if possible (Appendix 8). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is residing at the CRU, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for additional follow-up visit(s). All withdrawn subjects will be followed until resolution of all their adverse events or until the unresolved adverse events are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of adverse events thought to be related to the study drug will generally not be replaced.

4.6. Study Termination

The Sponsor may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice. Both the Sponsor and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The Investigator is to notify the Ethics Committee (EC) in writing of the study's completion or early termination and send a copy of the notification to the Sponsor. The Sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply investigational product and by what mechanism, after termination of the study.

In addition, the study may be terminated by the Sponsor at any time and for any reason. If the Sponsor decides to terminate the study, they will inform the Investigator as soon as possible.

5. STUDY TREATMENTS

Study treatment is defined as any investigational product, non-investigational product, placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as IMP and non-IMP, respectively.

5.1. Investigational Product

The IMP will be supplied by the Sponsor. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of the IMP shown in Table 1.

All supplies of investigational product, both bulk and subject-specific, will be stored in accordance with the manufacturer's instructions or pharmacy instructions. Until dispensed to the subjects, the IMP will be stored at the study site in a location that is locked with restricted access.

The IMP (solution containing CCI AMG 592) will be supplied by the Sponsor (or designee), along with the lot numbers and Certificates of Analysis. The IMP will be stored according to the instructions on the label.

Table 1: Investigational Product

	Investigational Medicinal Product:
Study Treatment Name	AMG 592
Unit Strength and Formulation	CCI
Dosage Level	CCI
Route of Administration	Subcutaneous injection
Accountability	The quantity administered, date administered, and lot number of the investigational medicinal product are to be recorded on each subject's electronic case report form.
Dosing Instructions	Treatment will be administered after the completion of all predose procedures.

5.2. Investigational Product Administration

Each SC injection will be administered by qualified and appropriately trained clinical staff to the lower abdomen. There are no posture requirements for dosing.

5.3. Treatment of Overdose

Neither the effects of overdose of AMG 592 nor an antidote to overdose are known.

5.3.1. Medical Devices

No investigational medical device will be used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care. Non-investigational medical devices (eg, syringes, sterile needles) that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

5.3.2. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either the Sponsor or by distributors and partners for whom the Sponsor manufactures the material. This includes any investigational product (AMG 592) provisioned and/or repackaged/modified by the Sponsor.

Any product complaint(s) associated with an investigational product (AMG 592) supplied by the Sponsor are to be reported according to the instructions provided in the Amgen IPIM.

5.4. Randomization

This study will not be randomized.

5.5. Blinding

This is an open-label study.

5.6. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- At each dosing occasion, a predose and postdose inventory of AMG 592 will be performed.

5.7. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of AMG 592 received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused AMG 592 will be returned to the Sponsor, retained at the study site, or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the EOS visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Acetaminophen (paracetamol) (2 g/day), hormone replacement therapy or oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an adverse event. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

Subjects will be required to fast from food overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations. Water may be consumed ad libitum throughout the study.

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

Foods and beverages containing poppy seeds will not be allowed from 7 days prior to Check-in until after the EOS visit.

Caffeine-containing foods and beverages will not be allowed from 24 hours prior to each clinic visit and while at the CRU.

Consumption of alcohol will not be permitted from 48 hours prior to each clinic visit. Alcohol intake will be limited to a maximum of 1 unit/day on all other days, while not in the CRU, from Screening through the EOS visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 6 months prior to Check-in until after the EOS visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before Check-in until after the EOS visit. Subjects will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, and platelets from 6 weeks prior to Check-in until 3 months after the EOS visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- PK blood samples
- safety assessments (ECGs will be scheduled before vital signs measurements)
- any other procedures.

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, safety laboratory assessments, and assessment of adverse events and serious adverse events.

Any blood sample collected according to the Schedule of Assessments (Appendix 8) can be analyzed for any of the tests outlined in the protocol and for any tests

necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 8. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Serum concentrations of AMG 592 will be determined using validated analytical procedures. Specifics of the analytical method will be provided in a separate document.

CCI [redacted]

7.3. Anti-AMG 592 and Anti-IL-2 Assessments

Blood samples for antibody testing are to be collected at the times listed in the Schedule of Assessments (Appendix 8). Samples testing positive for anti-AMG 592 and/or anti-IL-2 antibodies will also be tested for neutralizing antibodies and may be further characterized. More frequent testing or testing for a longer period of time may be required in the event of a safety-related concern.

Subjects who test positive at the EOS timepoint for neutralizing antibodies to IL-2 or binding antibodies with potentially antibody-mediated clinical sequelae will be asked to return for follow-up testing. This testing is to occur approximately every 3 months starting from the EOS visit and continue until: 1) antibodies are no longer detectable or 2) the subject has been followed for a period of at least 12 months (± 4 weeks) post administration of AMG 592 (whichever is shorter). All follow-up results, both positive and negative, will be communicated to the study site.

7.4. Biomarker Development

7.4.1. Blood Samples for Biomarker Development

Blood samples for biomarker development will be collected at the times indicated in the Schedule of Assessments in Appendix 8. Procedures for collection, processing, and shipping of biomarker development samples will be detailed in a separate document.

7.4.2. Analytical Methodology

Blood samples for biomarker development may be used to explore possible relationships between exposure to AMG 592 and physiological responses in individual subjects or in the general population, as part of the overall development program for AMG 592. Specifics of the analytical methods will be provided in a separate document.

7.5. Safety and Tolerability Assessments

7.5.1. Adverse Events and Serious Adverse Events: Time Period and Frequency for Collecting and Reporting Safety Event Information

Adverse event definitions, assignment of severity and causality, and procedures for reporting serious adverse events are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to the EOS.

If an event is reported as beginning prior to signing of the ICF or occurs prior to initiation of study treatment on Day 1 and is assessed as not related to study procedures by the Investigator (or designee), the event will be recorded as subject medical history. Any events prior to study drug administration but deemed by the Investigator to be related to study procedures will be reported as adverse events. Any events occurring after study drug administration on Day 1 through the EOS visit will be reported as adverse events.

Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report adverse events occurring at any other time during the study.

Adverse Events

The adverse event grading scale to be used in this study is described in Appendix 1.

The Investigator is responsible for ensuring that all non-serious adverse events observed by the Investigator or reported by the subject (whether reported by the subject voluntarily or upon questioning, or noted on PE) from enrollment through the EOS visit are recorded/reported using the appropriate eCRF.

Serious Adverse Events

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of the ICF through 30 days after the last dose of study treatment or the EOS visit (whichever is later) are reported using the appropriate eCRF and reported on the paper-based Serious Adverse Event Report Form (described in Appendix 1).

All serious adverse events will be collected, recorded, and reported to the Sponsor within 24 hours of the Investigator's knowledge of the event. The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, Investigators are required to report serious adverse events that they become aware of after the EOS visit. If serious adverse events are reported, the Investigator is to report them to the Sponsor within 24 hours following the Investigator's knowledge of the event using the paper-based Serious Adverse Event Report Form.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the Sponsor's safety database as clinical trial cases and handled accordingly based on relationship to the investigational product.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed, where possible, until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up. This will be completed at the Investigator's (or designee's) discretion.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the eCRF.

Regulatory Reporting Requirements for Serious Adverse Events

If the subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.

Prompt notification by the Investigator to the Sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, ECs, and Investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the Sponsor will file it along with the IB and will notify the EC, if appropriate according to local requirements.

Safety Monitoring Plan

Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.

Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and pregnancies in female partners of male subjects will be collected after the start of study treatment and until 90 days after the dosing.

If a pregnancy and/or lactation is reported, the Investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow up with the Investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

7.5.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 8. Clinical laboratory evaluations are listed in Appendix 2.

The Investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in CRF/eCRF. The Investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse

events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 8. For all female subjects, a pregnancy test and follicle-stimulating hormone screen for postmenopausal status will be performed at the times indicated in the Schedule of Assessments in Appendix 8.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.5.3. Vital Signs

Supine BP, supine heart rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 8. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be supine for at least 5 minutes before BP and heart rate measurements. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as possible, but prior to the blood draw.

7.5.4. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 8. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF >500 msec
- QTcF change from the baseline (predose) is >60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.5.5. Physical Examination

A full PE or symptom-directed PE will be performed at the timepoints specified in the Schedule of Assessments in Appendix 8. The PE will also include a neurological exam. The neurological examination should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

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

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

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

8.2.2. Pharmacodynamic Population

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

8.2.3. 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.

8.3. Pharmacokinetic Analyses

The serum PK parameters of AMG 592 will be calculated using standard noncompartmental methods.

The primary PK parameters are C_{max}, t_{max}, AUC_{last}, and AUC_{inf} for AMG 592. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis.

Additional PK parameters may be calculated. Specific details will be presented in the Statistical Analysis Plan for this study.

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

8.5. Anti-AMG 592 and Anti-IL-2 Analyses

The formation of anti-AMG 592 and anti-IL-2 antibodies will be summarized descriptively. The incidence and percentage of subjects who develop antidrug antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

8.6. Safety Analysis

The number and percentage of subjects reporting any adverse events will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

No imputation will be done for safety assessments, and endpoints for clinical laboratory tests and vital signs will be summarized.

8.7. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

1. Amgen, Inc. Efavaleukin Alfa (AMG 592; Inflammatory Diseases) – Investigator's Brochure. (Version 5.0). 17 December 2020.

2. Yu A, Snowhite I, Vendrame F, et al. Selective IL-2 responsiveness of regulatory T cells through multiple intrinsic mechanisms support the use of low-dose IL-2 therapy in Type-1 diabetes. *Diabetes*. Published online: 09 January 2015 (doi: 10.2337/db 14-1322).

3. Gavin MA, Rasmussen JP, Fontenot JD, et al. Foxp3-dependent programme of regulatory T cell differentiation. *Nature*. 2007;445:771-775.

4. Fontenot JD, Rasmussen JP, Gavin MA, Rudensky AY. A function to interleukin 2 in Foxp3-expressing regulatory T cells. *Nature Immunol*. 2005;6:1142-1151.

10. APPENDICES

Appendix 1: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device, or procedure. • Note: Treatment-emergent adverse event will be defined in the Statistical Analysis Plan.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect

Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant adverse event/serious adverse event information in the event electronic case report form (eCRF).
- The Investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to the investigational product(s) and/or study-mandated procedures, and
  - Action taken.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the appropriate eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor in lieu of completion of the appropriate eCRF page.

- If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The Investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will use the following definitions:

Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated, usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	Discomfort enough to cause interference with usual activity causing discomfort but poses no significant or permanent risk of harm to the subject. Usually alleviated with additional specific therapeutic intervention.
SEVERE[a]	Incapacitating with inability to work or interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

[a] An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between investigational product(s), protocol-required therapy and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the Investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.
    - If a subject dies during participation in the study, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper Serious Adverse Event Report Form
• Facsimile transmission of the Serious Adverse Event Report Form (see Figure 2) is the preferred method to transmit this information. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.

Figure 2: Sample Serious Adverse Event Report Form

AMGEN 20200102 LabCorp Study # 8448873 AMG 592	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

Amgen (Sponsor) UK Safety Fax Number: + 0800 028 4223
If FAX is unavailable, email form to the following address: svc-ags-in-gb@amgen.com

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		❑F ❑M		

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____ Month____ Year____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by IP or an Amgen device used to administer the IP? If yes see section 10 AMG592 No/Yes <<Device>> No/Yes <<Device>> No/Yes <<Device>> No/Yes <<Device>> No/Yes	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: **01** Fatal; **02** Immediately life- threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other medically important serious event

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ❑No ❑Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 592 ❑Blinded ✔Open Label							Lot #_____ ❑ Unknown Serial #_____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot #_____ ❑ Unknown Serial #_____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot #_____ ❑ Unknown Serial #_____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot #_____ ❑ Unknown Serial_____ ❑ Unknown

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AMGEN 20200102 LabCorp Study # 8448873 AMG 592	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	Site Number	Subject ID Number	

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN 20200102 LabCorp Study # 8448873 AMG 592	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

	Site Number	Subject ID Number	

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*	Title	Date

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Bilirubin[a] Gamma-glutamyl transferase Glucose HbA1C Inorganic phosphate Potassium QuantiFERON-TB Gold test Sodium Total CO_2 (measured as bicarbonate) Total creatine kinase Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Serology[b]:	**Drug screen[c]:**	**Hormone panel - females only:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test Alcohol breath test	Follicle-stimulating hormone[b] Serum pregnancy test (human chorionic gonadotropin)[d] Urine pregnancy test[d]
		Other Tests:
		Hepatotoxicity only: International normalized ratio (INR)[e] Estimated glomerular filtration rate(eGFR)[f] Creatine kinase MB fraction[c]

[a] Includes total, direct, and indirect.
[b] Only analyzed at Screening.
[c] Only analyzed at Screening and Check-in.
[d] Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[e] International normalized ratio will be tested if hepatotoxicity is suspected, per guidelines presented in Appendix 7.
[f] Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease equation.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations	7.5	6	45
Serology	3.5	1	3.5
AMG 592 pharmacokinetics	3.5	15	52.5
Lymphocyte subsets	9	6	54
Biomarker development samples	5	7	35
Anti-AMG 592 and anti-IL-2 Antibodies	3.5	4	14
Total:			204

FSH = follicle-stimulating hormone; IL-2 = interleukin 2

If additional blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: Contraception Requirements

All subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they conceive a child during treatment and for 90 days after the end of study (EOS) visit.

Additional medications given during the study may alter the contraceptive requirements. The Investigator must discuss these contraceptive changes with the subject.

Definitions

Women of Childbearing Potential:

Premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Non-Childbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Requirements

Female Subjects

Female subjects who are of non-childbearing potential will not be required to use contraception.

Female subjects of childbearing potential must be willing to use 2 methods [1 primary (highly effective) and 1 secondary method] of birth control from the time of signing the informed consent form until 90 days after the EOS visit.

Primary (highly effective) methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill associated with inhibition of ovulation (as prescribed) without supplementary iron (ie, Loestrin Fe, Junel Fe, and Lo Loestrin Fe are prohibited)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
    - Bilateral tubal ligation with confirmation of surgical success
    - Regulatory approved method of hysteroscopic bilateral tubal occlusion with confirmation of occlusion of the fallopian tubes
- hormonal implant
- hormonal or non-hormonal intrauterine device (IUD or IUS)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects should refrain from donation of ova from Check-in (Day -1) until 90 days after the EOS visit.

Male Subjects:

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception by female partner from Check-in until 90 days after the EOS visit. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or regulatory approved method of hysteroscopic bilateral tubal occlusion)
- hormonal implant
- hormonal or non-hormonal IUD
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide.

Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the EOS visit.

Sexual Abstinence

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the informed consent form (ICF) until 90 days after the EOS visit.

Same-sex Relationships

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the EOS visit.

Appendix 5: Collection of Pregnancy and Lactation Information

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 90 days after EOS.
- Information will be recorded on the Pregnancy Notification Form (see Figure 3). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 90 days after EOS. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse events or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to the Sponsor as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly), the Investigator will report the event as a serious adverse event.

- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator will be reported to Amgen Global Patient Safety as described in Appendix 1. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 4.5 for details).

Male Subjects with Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 90 days after EOS, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 3) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The Investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- The Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 90 days after the EOS.

- Information will be recorded on the Lactation Notification Form (Figure 4) and submitted to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event.
- Study treatment will be discontinued if the female subject breastfeeds during the study.

With the female subject's signed authorization for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 90 days after discontinuing protocol-required therapies.

Figure 3: Pregnancy Notification Form

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20200102 LabCorp # 8448873_____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Figure 4: Lactation Notification Form

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20200102 LabCorp # 8448873_____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐Yes ☐No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
- Notifying the EC of serious adverse events or other significant safety findings as required by EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

An initial sample ICF will be provided for the Investigator (or designee) to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Study Manager to the Investigator. The written ICF is to be prepared in the language(s) of the potential study participant population.

The Investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and the Ethics Committee (EC) or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 21 days from the previous ICF signature date.

Subject Data Protection

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to the Sponsor.

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic case report form (eCRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to the Sponsor, subjects are to be identified by their unique subject identification number, (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to the Sponsor (eg, signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the EC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential information of the Sponsor, Amgen Inc. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written permission from the Sponsor.

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic CRF (eCRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the Investigator, except as described below.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- The contract research organization (CRO) is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify

the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

The policy for publication of data obtained during this study will be documented in the clinical study agreement.

Appendix 7: Hepatotoxicity: Suggested Actions and Follow-up Assessments

Subjects with normal hepatic function at Screening who experience aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3 x upper limit of normal (ULN) or subjects with elevated values before drug exposure who have a 2-fold increase above baseline values (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009) are to undergo clinical assessments and a period of "close observation" until abnormalities return to normal or to the subject's baseline level as described below.

Clinical Assessments and Observation

Assessments that are to be performed during this period include:

- Repeat AST, ALT, alkaline phosphatase, bilirubin (total and direct), and international normalized ratio (INR) within 24 hours
- In cases of total bilirubin (TBL) > 2 x ULN or INR > 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever

    - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
    - Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or are considered stable by the Investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential drug-induced liver injury (DILI) event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding electronic case report form (eCRF).

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms

- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis).

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, ie, cases of AST or ALT > 3 x ULN and concurrent TBL > 2 x ULN or INR > 1.5 (for subjects not on anticoagulation therapy) without evidence of alternative cause of the elevations, require the following:

- The event is to be reported to the Sponsor as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate eCRF captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Sponsor.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 1.

Appendix 8: Schedule of Assessments

PROCEDURE	Screening	Check-in		Treatment Period														
		Resident at the Clinical Research Unit																
Study Day	**-28 to -2**	**-1**	**1**	**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**11**	**15**	**22**	**29**	**43[a] (EOS)/ET**
Relative to Dosing (Hours)			**Pre**	**0**	**6**	**12**	**16**	**24**	**48**	**72**	**96**	**120**	**168**	**240**	**336**	**504**	**672**	**1008**
GENERAL AND SAFETY ASSESSMENTS																		
Informed Consent	X																	
In-house Residency[b]		◄	─	─	─	─	─	─	►	◄	- -	- -	- -	►				
Physical Examination[c]	X	X							X					X		X	X	X
Medical History	X	X[d]																
Weight	X																	
Height	X																	
ECG[e]	X	X																
Vital Signs[f]	X	X	X					X	X			X	X	X		X		X
Adverse Events[g]	◄	─	─	─	─	►												
Serious Adverse Events[h]	X	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	►
Concomitant Therapy Review[i]	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	►
LABORATORY ASSESSMENTS																		
Pregnancy Test[j]	X	X																X
Chemistry and Hematology[k]	X	X							X					X		X		X
Serology	X																	
Urinary Drug Screen	X	X																
Alcohol Breath Test	X	X																
Urinalysis	X	X							X					X		X		X
eGFR[l]	X	X																
FSH[m]	X																	
BIOMARKER AND IMMUNOLOGICAL ASSESSMENTS																		
Lymphocyte Subsets		X						X					X		X	X		X
Biomarker Development Samples		X			X	X							X		X	X		X
Anti-AMG 592 and Anti-IL-2 Antibodies		X													X		X	X
PHARMACOKINETIC ASSESSMENTS																		
AMG 592 Serum PK Collection[n]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
STUDY TREATMENT																		
AMG 592 Administration				X														

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = follicle-stimulating hormone; PE = physical examination; PK = pharmacokinetic

[a] Subjects who test positive at the EOS timepoint for neutralizing antibodies to IL-2 or binding antibodies with potentially antibody-mediated clinical sequelae that are considered potentially related to an anti-AMG 592 antibody response will be asked to return for additional follow-up testing every 3 months until antibodies are no longer detectable or up to 12 months' post administration of AMG 592 (whichever is shorter).

[b] Inhouse residency from Day 1 through the completion of all assessments on Day 3. Solid line indicates time that subjects are required to stay in the CRU. Dashed line indicates that subjects may stay in the CRU after Day 3 until a maximum of Day 11 if they choose (to reduce travel and accommodation burden on subjects); alternatively, the Investigator may require subjects to remain in-house for 1 or more days after Day 3 (up to Day 11) at their discretion, based on other signs and symptoms requiring monitoring.

[c] Physical examination to include a neurological examination. A full PE will be conducted at Screening. A symptom-directed PE will be conducted on Days -1, 3, 11, 22, 29, and 43/EOS.

[d] Interim medical history only.

[e] Electrocardiogram (ECG) will be single 12-lead ECG, prior to blood draws or invasive procedures.

[f] Supine blood pressure (BP), supine heart rate, respiratory rate, and oral body temperature. Heart rate and BP will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes.

[g] Adverse events will be recorded from initiation of study treatment on Day 1 until the EOS. Any events prior to study drug administration but deemed by the Investigator to be related to study procedures will be reported as adverse events.

[h] Serious adverse events will be recorded from the time the subject signs the informed consent form until the EOS.

[i] Prior and concomitant medication administration will be recorded beginning at informed consent. Also, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) before Day 1 for over-the-counter or prescription medications, and 30 days prior to Check-in for herbal medicines (eg, St. John's wort), vitamins, or supplements will be recorded on the subject's electronic case report form.

[j] Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

[k] Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations.

[l] The eGFR will be calculated using the Modification of Diet in Renal Disease equation.

[m] Performed in females only.

[n] Blood samples for determination of AMG 592 serum concentrations and PK parameters will be collected: Predose; 6, 12, and 16 hours postdose; and on Days 2 (24 hours postdose), 3, 4, 5, 6, 8, 11, 15, 22, 29, and 43 (EOS) following administration of AMG 592 on Day 1. The postdose samples collected on Days 1 and 2 (6, 12, 16, and 24 hour samples) will have a sampling window of ± 30 minutes, postdose samples collected on Days 3 and 4 will have a sampling window of ± 6 hours, postdose samples collected on Days 5 through Day 15 will have a sampling window of ± 1 day, postdose samples taken on Days 22 and 29 will have a sampling window of ± 2 days, and postdose samples taken on Day 43 (EOS) will have a sampling window of ± 4 days. Times of all PK samples will be recorded to the nearest minute.

Protocol

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

Protocol Status: Final
Protocol Date: 01 April 2021
Protocol Version: 1.0

Investigational Product: AMG 592 (efavaleukin alfa)

Amgen Protocol Reference Number: 20200102
Covance Study Number: 8448873
IND Number: 131270

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

Confidentiality Notice

INVESTIGATOR AGREEMENT

I have read the protocol entitled "A Phase 1, Open-label, Randomized, Parallel-arm, Single-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AMG 592 Administered Subcutaneously in Healthy Chinese, Japanese, and Caucasian Subjects," and agree to conduct the study as described herein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____

Signature

_____ _____

PPD Date (DD Month YYYY)

STUDY IDENTIFICATION

Sponsor	Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320
Sponsor's Study Contact	PPD
Medical Monitor	PPD
Sponsor's Study Manager	PPD
Covance Program Manager	PPD
Statistician	PPD

SYNOPSIS

Title of study: A Phase 1, Open-label, Randomized, Parallel-arm, Single-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AMG 592 Administered Subcutaneously in Healthy Chinese, Japanese, and Caucasian Subjects

Objectives:

The primary objective of the study is:

- to evaluate the pharmacokinetics (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-interleukin (IL)2 antibodies in healthy Chinese, Japanese, and Caucasian subjects after single SC administration of AMG 592.

CCI [redacted]

Study design:

This will be an open-label, partially randomized, single-dose, parallel-arm study in 2 groups of healthy Chinese subjects and 1 group of Japanese subjects. In addition, a group of Caucasian subjects will be evaluated at the high dose for comparison. Potential subjects will be screened within 28 days prior to the dose. Subjects will be admitted into the clinical research unit (CRU) on Day -1 and will be confined to the CRU until discharge on Day 3. Chinese subjects (n = CCI [redacted]) will be randomized in a 1:1 ratio to receive a single SC dose of AMG 592 at CCI [redacted] (Group 1) or CCI [redacted] (Group 2). Japanese subjects (n = CCI [redacted]) will receive a single SC dose of AMG 592 at CCI [redacted] (Group 3). Caucasian subjects (n = CCI [redacted]) will receive a single SC dose of AMG 592 at CCI [redacted] (Group 4). After discharge from the research facility, subjects will return to the CRU for outpatient visits on Days 4, 5, 6, 8, 11, 15, 22, 29, and at the end of study (EOS) visit on Day 43. A subject's participation in the study will conclude at the completion of the EOS visit; however, subjects who test positive at the EOS timepoint 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 from dosing (whichever is shorter).

Number of subjects:

Approximately 32 subjects (CCI [redacted] per group) will be enrolled in this study.

Diagnosis and main criteria for inclusion:

Healthy male or female subjects of Chinese ancestry, first- or second-generation Japanese subjects, and Caucasian subjects, 18 to 55 years of age (inclusive), body mass index of 17 to 30 kg/m^2 (inclusive).

Investigational products, dose, and mode of administration:

Investigational Medicinal Product: CCI [redacted] AMG 592 given as a CCI [redacted] SC injection, CCI [redacted] AMG 592 given as a CCI [redacted] SC injection.

Group 1 = CCI [redacted] SC
Group 2 = CCI [redacted] SC
Group 3 = CCI [redacted] SC
Group 4 = CCI [redacted] SC

Duration of subject participation in the study:

Planned Screening duration: approximately 4 weeks.
Planned study duration (Screening to EOS): approximately 10 weeks.

Primary endpoints:
The primary endpoints for this study are PK parameters: maximum observed serum concentration (C_{max}), the time of maximum observed serum concentration (t_{max}), area under the serum concentration-time curve (AUC) from time zero to time of last quantifiable concentration (AUC_{last}), and AUC from time zero to infinity (AUC_{inf}).

Secondary endpoints:
Secondary endpoints for this study are: treatment-emergent adverse events and serious adverse events (including clinically significant changes in physical examinations), clinical laboratory tests, vital signs, and anti-AMG 592 and anti-IL-2 antibody formation.

CCI [redacted]

Statistical methods:
Data will be analyzed for all subjects who were enrolled and received a dose of AMG 592. Descriptive statistics by treatment arm will be provided for selected demographics, safety, PK parameters, and PD and immunogenicity data. Descriptive statistics on continuous measurements will include geometric and arithmetic means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. The PK, vital signs, and clinical laboratory data will be summarized for each timepoint when samples are collected.
The final safety analysis for the study will be performed at the end of the study. Adverse events will be summarized using descriptive methodology. Each adverse event will be coded using the Medical Dictionary for Regulatory Activities. No imputation will be done for safety assessments, and endpoints for clinical laboratory tests and vital signs will be summarized. No inferential statistical analysis is planned.
Additional details will be included in the Statistical Analysis Plan.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC_{inf}	area under the serum concentration-time curve from time zero to infinity
AUC_{last}	area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AV	atrioventricular
BP	blood pressure
CD4	cluster of differentiation 4
CD25	alpha chain of the interleukin 2 receptor
CFR	Code of Federal Regulations
C_{max}	maximum observed serum concentration
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CRU	clinical research unit
DILI	drug-induced liver injury
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
FIH	first-in-human
FOXP3	forkhead box P3; an essential transcription factor of Treg function, upregulated by IL-2R signals
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GvHD	graft-versus-host disease
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IL	interleukin
IL-2R	interleukin 2 receptor
IL-2RA	interleukin 2 receptor alpha chain
IL-2RB	interleukin 2 receptor beta chain
ILC2	innate lymphoid cells
IMP	investigational medicinal product
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	institutional review board

IUD	intrauterine device
NK	natural killer
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic
PE	physical examination
PK	pharmacokinetic(s)
Q2W	every 2 weeks
QTcF	QT interval corrected for heart rate using Fridericia's method
QW	once weekly
RA	rheumatoid arthritis
SC	subcutaneous
SLE	systemic lupus erythematosus
$t_{1/2}$	terminal elimination half-life
TB	tuberculosis
TBL	total bilirubin
Tcon	conventional T cells
t_{max}	time of the maximum observed serum concentration
Tregs	regulatory T cells
ULN	upper limit of normal

1. INTRODUCTION

Refer to the Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational medicinal product (IMP).

1.1. Background

Investigational Medicinal Product

Regulatory T cells (Tregs) are a subset of cluster of differentiation 4 (CD4) T cells that suppress inflammation and whose numbers and function are maintained by interleukin (IL)-2. In addition to Treg, IL-2-responsive lymphocytes include conventional CD4 and CD8 T (Tcon) cells, natural killer (NK) cells, and innate lymphoid cells (ILC2). A loss in the homeostatic balance between Tregs and other lymphocytes is considered a causative factor in many inflammatory conditions.

AMG 592 (efavaleukin alfa) is an Fc-IL-2 mutein that contains 2 mutations in the IL-2 domain. To increase the Treg selectivity of IL-2, 1 mutation is in the region that binds the beta chain of the IL-2 receptor (IL-2RB). This mutation reduces its signaling potency and increases its dependence on expression of interleukin 2 receptor alpha chain (IL-2RA/CD25). It drives a positive feedback loop enforcing Treg phenotype, abundance, and IL-2 responsiveness over effects on other lymphocytes. The other mutation is in an internal region of IL-2 and improves manufacturability of AMG 592 but does not alter its biological activity.[2,3,4]

The IL-2R is composed of 3 chains: IL-2RB and IL-2R gamma, which together deliver the intracellular IL-2R signal, and IL-2RA (CD25), which stabilizes IL-2 association with IL-2RBG but does not contain a signaling domain. The alpha chain of the IL-2 receptor (CD25) is highly expressed on Treg, and IL-2R signaling in Treg promotes expression of both CD25 and FOXP3, the essential transcription factor for Treg development and function. High FOXP3 expression promotes both full Treg suppressor activity and high CD25 expression, resulting in a positive feedback loop enforcing Treg phenotype, abundance, and IL-2 responsiveness.[2,3,4]

The mutation in the IL-2RB-binding region of IL-2 results in increased dependence on CD25 for IL-2R signaling compared with wild-type IL-2. Thus, efavaleukin alfa preferentially drives this positive feedback loop in Treg over effects on other lymphocytes (ie, other T cells and ILC2 which may express CD25 but do not express FOXP3, and NK cells which express little or no CD25 and no FOXP3). Compared with aldesleukin, efavaleukin alfa exhibits greatly improved selectivity for Treg over Tcon and NK cells both in vitro and in vivo, potentially resulting in an improved therapeutic margin. In addition, the Fc domain of AMG 592 confers a prolonged half-life compared with aldesleukin, thus reducing the dosing frequency required to maintain Treg enrichment

Nonclinical in vitro and in vivo studies have demonstrated that AMG 592 exhibits greater selectivity for inducing Treg expansion over the expansion of CD4 and CD8 T cells, and NK cells, relative to low dose, recombinant IL-2. This greater selectivity of AMG 592 has promise for greater efficacy and a wider therapeutic margin in inflammatory diseases relative to low-dose recombinant IL-2-based modalities.

Amgen is developing AMG 592 as a treatment for multiple inflammatory diseases including systemic lupus erythematosus (SLE), steroid-refractory chronic graft-versus-host disease (GvHD), and ulcerative colitis. This study is designed to evaluate whether pharmacokinetic (PK) and safety data in Chinese and Japanese subjects are similar to those from the global population.

A summary of completed and ongoing clinical studies for AMG 592 is provided in the IB.[1]

1.2. Pharmacokinetics

In a first-in-human (FIH) study (Study 20140324), PK results of AMG 592 in healthy subjects following single-dose subcutaneous (SC) administration of AMG 592 are available for doses of CCI. Results show dose-related increases in AMG 592 serum exposure (as assessed by maximum observed concentration [C_{max}] and area under the serum concentration-time curve [AUC] from time zero to infinity [AUC_{inf}]) with approximately dose-proportional increase over the CCI CCI. Following SC administration, the median time to maximum observed serum concentration (t_{max}) ranged from approximately 0.5 to 1 day with terminal phase half-life ($t_{1/2}$) about 11 to 13 hours postdose at doses CCI.

In a single-dose PK study in healthy Japanese subjects (Study 20180132), exposure of AMG 592, assessed by C_{max} and AUC_{inf}, increased approximately dose proportionally over the CCI. Mean C_{max} and AUC_{inf} exhibited CCI. The median t_{max} was 14 hours in the AMG 592 CCI cohort and 24 hours in the AMG 592 CCI cohort. For the CCI cohort, the mean half-life, apparent drug clearance, volume of distribution, and mean residence time was 11.7 hours, 1.29 L/hour, 21.9 L, and 33.2 hours, respectively. For the CCI cohort, the mean half-life, apparent drug clearance, volume of distribution, and mean residence time was 9.68 hours, 0.852 L/hour, 11.7 L, and 39.5 hours, respectively.

In a multiple-dose study in patients with active rheumatoid arthritis (RA), exposure to AMG 592, as expressed in AUC and C_{max}, increased with increasing dose from CCI every 2 weeks (Q2W) to CCI once weekly (QW) to CCI Q2W. Peak concentrations were observed about 6 to 12 hours following dosing, with half-lives that ranged from about 10 to 40 hours. Moderate drug accumulation was observed for CCI Q2W and CCI QW. There were not enough data to determine the accumulation ratio for the CCI Q2W dose.

1.3. Study Rationale

The highest dose of AMG 592 previously evaluated in healthy Japanese and Caucasian subjects is CCI, and a dose of CCI has demonstrated Treg selectivity and acceptable safety in subjects with SLE. As AMG 592 has not previously been studied in healthy Chinese subjects, CCI was chosen as the low-dose level to permit direct comparison with results from previous studies. Chinese, Japanese, and Caucasian subjects were selected in order to allow comparison to previous data and extrapolation to future studies, to look for possible ethnic variation in PK or PD parameters, and as part of the effort to ensure that proper dose regimens are recommended for the appropriate patient populations of different

ethnicities. The current study should inform dose selection and design of future Phase 2 and 3 studies.

1.4. Benefit-risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study. Refer to the IB[1] for more information.

1.4.1. Therapeutic Context

1.4.1.1. Benefits

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study.

1.4.1.2. Risks

The safety of AMG 592 (efavaleukin alfa) has been studied in healthy volunteers and in SLE, chronic GvHD, and RA patients. Overall, approximately 143 subjects have been exposed to efavaleukin alfa in Amgen clinical studies. Single SC doses of up to CCI of efavaleukin alfa have been studied in healthy volunteers. Repeated SC doses of up to CCI of efavaleukin alfa administered Q2W have been studied in subjects with chronic GvHD over the course of a 52-week period. Doses up to CCI Q2W have been studied in subjects with SLE and up to CCI Q2W in subjects with RA over the course of a 12-week period. The safety profile of efavaleukin alfa is based on these clinical studies. Current adverse drug reactions reported in efavaleukin alfa clinical studies are erythema and pruritus, hypersensitivity, and RA. Potential risks are described in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to evaluate the PK of AMG 592 after single 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.

CCI

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints of the study are:

- C_{max}
- t_{max}
- AUC from time zero to time of last quantifiable concentration (AUC_{last})
- AUC_{inf}.

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

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

CCI [redacted]

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase 1, single-center, open-label, partially randomized, parallel-arm 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 [redacted] subjects in each of the 4 groups.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to dose administration. Eligible subjects will be admitted into the clinical research unit (CRU) for Check-in on Day -1 and be confined to the CRU until clinic discharge on Day 3. Each subject will participate in 1 treatment group only.

On Day 1, Chinese subjects (n = [redacted]) will be randomly assigned in a 1:1 ratio to either Group 1 or Group 2 by a Covance statistician. Japanese and Caucasian subjects will be assigned to Groups 3 and 4, respectively.

On Day 1, AMG 592 will be administered as a single SC injection.

- Group 1: Chinese subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted] SC injection
- Group 2: Chinese subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted] SC injection
- Group 3: Japanese subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted] SC injection
- Group 4: Caucasian subjects (n=[redacted]) will receive [redacted] AMG 592 given as one [redacted] SC injection

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

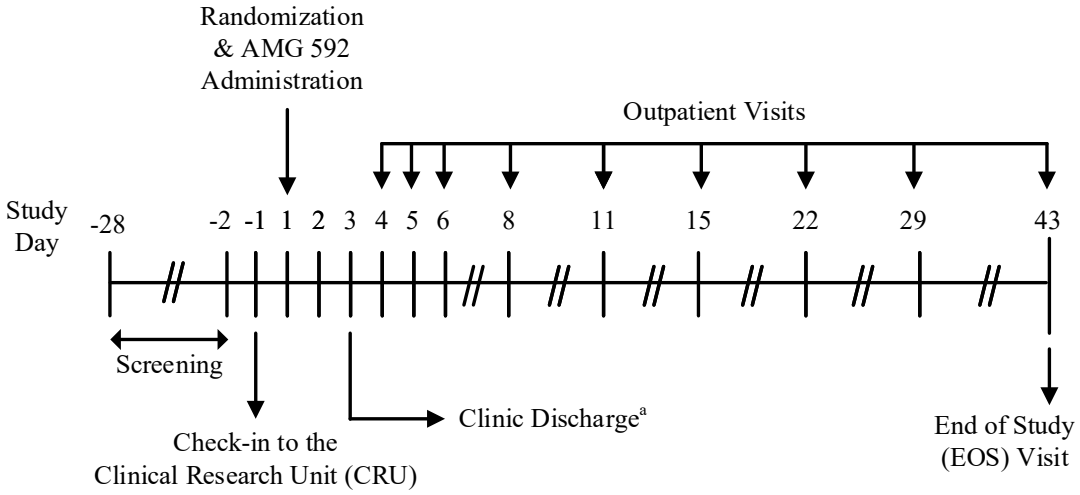
After discharge from the CRU, subjects will return for outpatient visits on Days 4, 5, 6, 8, 11, 15, 22, 29, and the end of study (EOS) visit on Day 43. It is anticipated that many subjects will be traveling a great distance to the CRU in order to participate in the study; therefore, to reduce unnecessary 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 3 through a maximum of Day 11. As this is for logistical purposes only, no additional study procedures are planned for subjects who decide to remain in the CRU, aside from the scheduled outpatient visit assessments on Days 4, 5, 6, 8, and 11. 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. A Schedule of Assessments is presented in Appendix 8.

Figure 1: Study Design



[a] Subjects may reside at the CRU after discharge on Day 3 until a maximum of Day 11, to reduce the travel and accommodation burden on subjects. For subjects who remain in the CRU after Day 3, no additional procedures are planned aside from the scheduled outpatient visit assessments on Days 4, 5, 6, 8, and 11.

3.2. Discussion of Study Design

This study is an open-label investigation because the study endpoints are not believed to be subject to bias.

This study will be partially randomized (Chinese subjects will be randomized in a 1:1 ratio to 1 of 2 dose levels) to ensure there is no bias when assigning subjects to each dose level.

Subcutaneous injection was chosen because this is the intended clinical route of administration.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

3.3. Selection of Doses in the Study

AMG 592 doses were selected based on safety, PK, and PD results from the completed FIH study (20140324), PK study in Japanese healthy subjects (20180132), multiple-dose study in RA patients, ongoing multiple SC dose Phase 1b studies in patients with chronic GvHD and patients with SLE, as well as results from GLP toxicology studies in cynomolgus monkeys. The high dose of CCI was chosen to evaluate the PK/PD response and because it is within the anticipated upper range of doses that will be used in Phase 2 and 3 studies. Results from Studies 20140324 and 20180132 as well as preliminary Phase 1b data indicate that AMG 592 is well tolerated at doses up to CCI with acceptable safety and Treg selectivity. Exposures in the present study are anticipated to be lower than those at the NOAEL (exposure multiples of at least 16.3 and 3 for AUC and C_{max}, respectively) in the 6-month repeat-dose GLP toxicology study in the cynomolgus monkey (Study 122293).

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria prior to enrollment, unless otherwise stated:

1. Subject has provided informed consent before initiation of any study-specific activities/procedures.
2. Healthy male or female subjects, between 18 and 55 years of age (inclusive) at the time of Screening.
3. Chinese, Japanese, or Caucasian subject:
    - Chinese subjects must be of Chinese ancestry (4 grandparents and biological parents).
    - Japanese subjects must be first- or second-generation Japanese (4 grandparents and biological parents; subject or both of their parents must have been born in Japan).
    - Caucasian subjects are those who self-identify exclusively as such on the electronic case report form (eCRF) and also identify their biological parents as such.
4. In good health, determined by no clinically significant findings from medical history, PE, 12-lead electrocardiogram (ECG), vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).
5. Body mass index between 17 and 30 kg/m^2 (inclusive) at the time of Screening.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria prior to enrollment unless otherwise stated:

1. History or evidence, at Screening or Check-in, of a clinically significant disorder, condition, or disease not otherwise excluded that, in the opinion of the Investigator (or designee), would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
2. Evidence of scars, tattoos, or other skin lesions that may interfere with the injection site or injection site assessments.
3. History or evidence of clinically significant arrhythmia at Screening, including any clinically significant findings on the ECG taken at Check-in.
4. A QT interval corrected for heart rate using Fridericia's method (QTcF) interval > 450 msec in male subjects or > 470 msec in female subjects or history/evidence of long QT syndrome, at Screening or Check-in.
5. PR interval > 210 msec, at Screening or Check-in.
6. Second- or third-degree atrioventricular (AV) block , at Screening or Check-in.

7. Systolic blood pressure (BP) > 140 mmHg or < 90 mmHg, or diastolic BP > 90 mmHg, or HR > 100 bpm, at Screening or Check-in.
8. History of hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee) and in consultation with the Sponsor.
9. Poor peripheral venous access.
10. Estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation, at Screening or Check-in.
11. Underlying condition that predisposes the subject to infections (eg, history of splenectomy).
12. HbA1C ≥ 7%, at Screening or Check-in.
13. Active tuberculosis (TB) requiring treatment or documented latent TB within the previous 3 years. All subjects will be required to have a QuantiFERON-TB Gold test performed at Screening. Also excluded are participants with evidence of a past TB infection without documented adequate therapy. Participants with a positive QuantiFERON-TB Gold test at Screening will not be eligible for the study. A QuantiFERON-TB Gold test performed within 4 weeks of dosing on Day 1 is acceptable as long as there is documentation of a negative result.
14. Subjects who have received live vaccines within 5 weeks prior to Screening, or plan to receive live vaccines within 105 days after administration of an investigational product.
15. Subjects who have received Coronavirus Disease 2019 (COVID-19) vaccine within 28 days prior to dosing, or plan to receive a COVID-19 vaccine within 28 days postdose; from 29 days postdose through EOS, vaccination for COVID-19 may be deemed acceptable for a subject following discussion and agreement between the sponsor and the investigator.
16. History of active infections (viral, bacterial, or fungal) within 21 days of receiving the investigational product.
17. Positive hepatitis B or hepatitis C panel and/or positive human immunodeficiency virus test, at Screening. Subjects whose results are compatible with prior vaccination may be included.
18. Use of any over-the-counter or prescription medications within 30 days or 5 half-lives (whichever is longer) of Check-in. Continued use, if applicable, will be reviewed by the Investigator (or designee) and in consultation with the Sponsor. Written documentation of this review and Sponsor acknowledgment is required for subject participation. Exceptions are listed below.
    - Acetaminophen [paracetamol] up to 2 g per day for analgesia will be allowed.
    - Hormonal contraception listed in Appendix 4 will be allowed.
    - Hormone replacement therapy (eg, estrogen) will be allowed.

19. Use of any herbal medicines, vitamins, or supplements consumed within the 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.
20. Consumption of foods and beverages containing poppy seeds within 7 days prior to Check-in.
21. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
22. Alcohol consumption from 48 hours prior to Check-in.
23. Regular alcohol consumption of > 14 units per week for males and > 7 units for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
24. Use of tobacco- or nicotine-containing products within 6 months prior to Check-in.
25. Positive test for illicit drugs, cotinine (tobacco or nicotine use), and/or alcohol use at Screening or Check-in.
26. Consumption of caffeine-containing foods and beverages within 24 hours prior to Check-in.
27. Female subjects with a positive pregnancy test at Screening or Check-in.
28. Female subjects who are lactating/breastfeeding or who plan to breastfeed during the study through 90 days after the EOS visit.
29. Subjects who are unwilling to adhere to contraceptive requirements through 90 days after the EOS visit (see Appendix 4).
30. Subjects who are unwilling to abstain from sperm donation and ovum donation from Check-in until 90 days after the EOS visit (see Appendix 4).
31. Male subject with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
32. Male subject with a pregnant partner or partner planning to become pregnant while the subject is on study through 90 days after the EOS visit.
33. Subject has received a dose of an investigational drug within the past 90 days or 5 half-lives of the drug, whichever is longer, prior to Check-in.
34. Subjects who have previously completed or withdrawn from this study or any other study investigating AMG 592 or have previously received the investigational product.
35. Donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, or platelets from 6 weeks prior to Check-in.
36. Subjects who are unwilling to abide with study restrictions.
37. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

4.3. Screen Failures and Rescreening

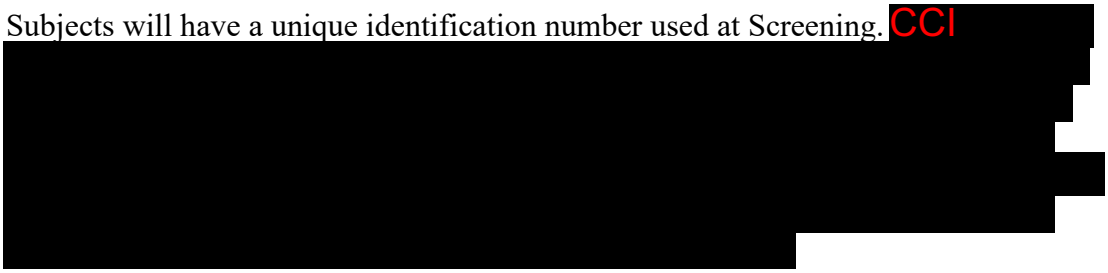
Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study because they do not meet eligibility requirements. A minimal set of screen failure information will be collected that

includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Subjects who have a screening laboratory test result that is out of range may have the test repeated once, and the subject may be enrolled if the repeated value is within range. This can be applied to any or all of the laboratory tests included in the exclusion criteria, and it can be disallowed for any critical tests at the discretion of the Investigator or Sponsor.

4.4. Subject Number and Identification

Subjects will have a unique identification number used at Screening. CCI



Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.5. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's eCRF, and efforts will be made to perform all EOS assessments, if possible (Appendix 8). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is residing at the CRU, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for additional follow-up visit(s). All withdrawn subjects will be followed until resolution of all their adverse events or until the unresolved adverse events are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of adverse events thought to be related to the study drug will generally not be replaced.

4.6. Study Termination

The Sponsor may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice. Both the Sponsor and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The Investigator is to notify the Ethics Committee (EC) in writing of the study's completion or early termination and send a copy of the notification to the Sponsor. The Sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply investigational product and by what mechanism, after termination of the study.

In addition, the study may be terminated by the Sponsor at any time and for any reason. If the Sponsor decides to terminate the study, they will inform the Investigator as soon as possible.

5. STUDY TREATMENTS

Study treatment is defined as any investigational product, non-investigational product, placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as IMP and non-IMP, respectively.

5.1. Investigational Product

The IMP will be supplied by the Sponsor. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of the IMP shown in Table 1.

All supplies of investigational product, both bulk and subject-specific, will be stored in accordance with the manufacturer's instructions or pharmacy instructions. Until dispensed to the subjects, the IMP will be stored at the study site in a location that is locked with restricted access.

The IMP (solution containing CCI AMG 592) will be supplied by the Sponsor (or designee), along with the lot numbers and Certificates of Analysis. The IMP will be stored according to the instructions on the label.

Table 1: Investigational Product

	Investigational Medicinal Product:
Study Treatment Name	AMG 592
Unit Strength and Formulation	CCI
Dosage Level	CCI
Route of Administration	Subcutaneous injection

Study Treatment Name	**Investigational Medicinal Product:** AMG 592
Accountability	The quantity administered, date administered, and lot number of the investigational medicinal product are to be recorded on each subject's electronic case report form.
Dosing Instructions	Treatment will be administered after the completion of all predose procedures.

5.2. Investigational Product Administration

Each SC injection will be administered by qualified and appropriately trained clinical staff to the lower abdomen. There are no posture requirements for dosing.

5.3. Treatment of Overdose

Neither the effects of overdose of AMG 592 nor an antidote to overdose are known.

5.3.1. Medical Devices

No investigational medical device will be used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care. Non-investigational medical devices (eg, syringes, sterile needles) that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

5.3.2. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either the Sponsor or by distributors and partners for whom the Sponsor manufactures the material. This includes any investigational product (AMG 592) provisioned and/or repackaged/modified by the Sponsor.

Any product complaint(s) associated with an investigational product (AMG 592) supplied by the Sponsor are to be reported according to the instructions provided in the Amgen IPIM.

5.4. Randomization

This study will be partially randomized (only Chinese subjects will be randomized to 1 of 2 dose levels) to ensure there is no bias when assigning subjects to each dose level. The randomization code will be produced by a Covance Statistician.

Prior to the start of the study, a copy of the master randomization code will be supplied to the Covance CRU pharmacy staff.

5.5. Blinding

This is an open-label study.

5.6. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- At each dosing occasion, a predose and postdose inventory of AMG 592 will be performed.

5.7. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of AMG 592 received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused AMG 592 will be returned to the Sponsor, retained at the study site, or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the EOS visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Acetaminophen (paracetamol) (2 g/day), hormone replacement therapy or oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an adverse event. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

Subjects will be required to fast from food overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations. Water may be consumed ad libitum throughout the study.

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

Foods and beverages containing poppy seeds will not be allowed from 7 days prior to Check-in until after the EOS visit.

Caffeine-containing foods and beverages will not be allowed from 24 hours prior to each clinic visit.

Consumption of alcohol will not be permitted from 48 hours prior to each clinic visit. Alcohol intake will be limited to a maximum of 1 unit/day on all other days, while not in the CRU, from Screening through the EOS visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 6 months prior to Check-in until after the EOS visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before Check-in until after the EOS visit. Subjects will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, and platelets from 6 weeks prior to Check-in until 3 months after the EOS visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- PK blood samples
- safety assessments (ECGs will be scheduled before vital signs measurements)
- any other procedures.

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, safety laboratory assessments, and assessment of adverse events and serious adverse events.

Any blood sample collected according to the Schedule of Assessments (Appendix 8) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 8. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Serum concentrations of AMG 592 will be determined using validated analytical procedures. Specifics of the analytical method will be provided in a separate document.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3. Anti-AMG 592 and Anti-IL-2 Assessments

Blood samples for antibody testing are to be collected at the times listed in the Schedule of Assessments (Appendix 8). Samples testing positive for anti-AMG 592 and/or anti-IL-2 antibodies will also be tested for neutralizing antibodies and may be further characterized. More frequent testing or testing for a longer period of time may be required in the event of a safety-related concern.

Subjects who test positive at the EOS timepoint for neutralizing antibodies to IL-2 or binding antibodies with potentially antibody-mediated clinical sequelae will be asked to return for follow-up testing. This testing is to occur approximately every 3 months starting from the EOS visit and continue until: 1) antibodies are no longer detectable or 2) the subject has been followed for a period of at least 12 months (+/- 4 weeks) post administration of AMG 592 (whichever is shorter). All follow-up results, both positive and negative, will be communicated to the study site.

7.4. Biomarker Development

7.4.1. Blood Samples for Biomarker Development

Blood samples for biomarker development will be collected at the times indicated in the Schedule of Assessments in Appendix 8. Procedures for collection, processing, and shipping of biomarker development samples will be detailed in a separate document.

7.4.2. Analytical Methodology

Blood samples for biomarker development may be used to explore possible relationships between exposure to AMG 592 and physiological responses in individual subjects or in the general population, as part of the overall development program for AMG 592. Specifics of the analytical methods will be provided in a separate document.

7.5. Safety and Tolerability Assessments

7.5.1. Adverse Events and Serious Adverse Events: Time Period and Frequency for Collecting and Reporting Safety Event Information

Adverse event definitions, assignment of severity and causality, and procedures for reporting serious adverse events are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to the EOS.

If an event is reported as beginning prior to signing of the ICF or occurs prior to initiation of study treatment on Day 1 and is assessed as not related to study procedures by the Investigator (or designee), the event will be recorded as subject medical history. Any events prior to study drug administration but deemed by the Investigator to be related to study procedures will be reported as adverse events. Any events occurring after study drug administration on Day 1 through the EOS visit will be reported as adverse events.

Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report adverse events occurring at any other time during the study.

Adverse Events

The adverse event grading scale to be used in this study is described in Appendix 1.

The Investigator is responsible for ensuring that all non-serious adverse events observed by the Investigator or reported by the subject (whether reported by the subject voluntarily or upon questioning, or noted on PE) from enrollment through the EOS visit are recorded/reported using the appropriate eCRF.

Serious Adverse Events

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of the ICF through 30 days after the last dose of study treatment or the EOS visit (whichever is later) are reported using the appropriate eCRF and reported on the paper-based Serious Adverse Event Report Form (described in Appendix 1).

All serious adverse events will be collected, recorded, and reported to the Sponsor within 24 hours of the Investigator’s knowledge of the event. The Investigator will

submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, Investigators are required to report serious adverse events that they become aware of after the EOS visit. If serious adverse events are reported, the Investigator is to report them to the Sponsor within 24 hours following the Investigator's knowledge of the event using the paper-based Serious Adverse Event Report Form.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the Sponsor's safety database as clinical trial cases and handled accordingly based on relationship to the investigational product.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed, where possible, until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up. This will be completed at the Investigator's (or designee's) discretion.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the eCRF.

Regulatory Reporting Requirements for Serious Adverse Events

If the subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.

Prompt notification by the Investigator to the Sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, ECs, and Investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the Sponsor will file it along with the IB and will notify the EC, if appropriate according to local requirements.

Safety Monitoring Plan

Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.

Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and pregnancies in female partners of male subjects will be collected after the start of study treatment and until 90 days after the dosing.

If a pregnancy and/or lactation is reported, the Investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow up with the Investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

7.5.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 8. Clinical laboratory evaluations are listed in Appendix 2.

The Investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in CRF/eCRF. The Investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 8. For all female subjects, a pregnancy test and follicle-stimulating hormone screen for postmenopausal status will be performed at the times indicated in the Schedule of Assessments in Appendix 8.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.5.3. Vital Signs

Supine BP, supine heart rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 8. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be supine for at least 5 minutes before BP and heart rate measurements. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as possible, but prior to the blood draw.

7.5.4. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 8. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF >500 msec
- QTcF change from the baseline (predose) is >60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.5.5. Physical Examination

A full PE or symptom-directed PE will be performed at the timepoints specified in the Schedule of Assessments in Appendix 8. The PE will also include a neurological exam. The neurological examination should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

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 CCI chance of CCI [redacted] experiencing an adverse event with a true incidence rate of CCI [redacted] chance of CCI [redacted] experiencing an adverse event with CCI 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.

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

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

8.2.2. Pharmacodynamic Population

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

8.2.3. 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.

8.3. Pharmacokinetic Analyses

The serum PK parameters of AMG 592 will be calculated using standard noncompartmental methods.

The primary PK parameters are C_{max}, t_{max}, AUC_{last}, and AUC_{inf} for AMG 592. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis.

Additional PK parameters may be calculated. Specific details will be presented in the Statistical Analysis Plan for this study.

[redacted]

8.5. Anti-AMG 592 and Anti-IL-2 Analyses

The formation of anti-AMG 592 and anti-IL-2 antibodies will be summarized descriptively. The incidence and percentage of subjects who develop antidrug antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

8.6. Safety Analysis

The number and percentage of subjects reporting any adverse events will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

No imputation will be done for safety assessments, and endpoints for clinical laboratory tests and vital signs will be summarized.

8.7. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

1. Amgen, Inc. Efavaleukin Alfa (AMG 592; Inflammatory Diseases) – Investigator's Brochure. (Version 5.0). 17 December 2020.

2. Yu A, Snowhite I, Vendrame F, et al. Selective IL-2 responsiveness of regulatory T cells through multiple intrinsic mechanisms support the use of low-dose IL-2 therapy in Type-1 diabetes. *Diabetes*. Published online: 09 January 2015 (doi: 10.2337/db 14-1322).

3. Gavin MA, Rasmussen JP, Fontenot JD, et al. Foxp3-dependent programme of regulatory T cell differentiation. *Nature*. 2007;445:771-775.

4. Fontenot JD, Rasmussen JP, Gavin MA, Rudensky AY. A function to interleukin 2 in Foxp3-expressing regulatory T cells. *Nature Immunol*. 2005;6:1142-1151.

10. APPENDICES

Appendix 1: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device, or procedure. • Note: Treatment-emergent adverse event will be defined in the Statistical Analysis Plan.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect

Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant adverse event/serious adverse event information in the event electronic case report form (eCRF).
- The Investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to the investigational product(s) and/or study-mandated procedures, and
  - Action taken.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the appropriate eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor in lieu of completion of the appropriate eCRF page.

- If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The Investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will use the following definitions:

Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated, usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	Discomfort enough to cause interference with usual activity causing discomfort but poses no significant or permanent risk of harm to the subject. Usually alleviated with additional specific therapeutic intervention.
SEVERE[a]	Incapacitating with inability to work or interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

[a] An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between investigational product(s), protocol-required therapy and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the Investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.
    - If a subject dies during participation in the study, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper Serious Adverse Event Report Form
• Facsimile transmission of the Serious Adverse Event Report Form (see Figure 2) is the preferred method to transmit this information. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.

Figure 2: Sample Serious Adverse Event Report Form

A 20200102 Covance Study#: 8448873 AMG 592	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

Amgen (Sponsor) UK Safety Fax Number: + 0800 028 4223
If FAX is unavailable, email form to the following address: svc-ags-in-gb@amgen.com

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number ( )	Fax Number ( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex ❑F ❑M	Race	If applicable, provide End of Study date

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day_____Month____Year_____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by IP (AMG 592) or an Amgen device used to administer the IP? If yes see section 10 AMG 592 No✓ Yes✓	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: **01** Fatal; **02** Immediately life- threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other medically important serious event

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ❑No ❑Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 592 ☑ Open Label							Lot # _____ ❑ Unknown Serial # _____ ❑ Unknown

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 *SAER Created: 08-MARCH-2021*
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A 20200102 Covance Study#: 8448873 AMG 592	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	Site Number	Subject ID Number	

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

A 20200102 Covance Study#: 8448873 AMG 592	**Clinical Trial Serious Adverse Event Report – Phase 1–4** ***Notify Amgen Within 24 Hours of knowledge of the event***	❑New ❑Follow-up

	Site Number	Subject ID Number	

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*	Title	Date

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Bilirubin[a] Gamma-glutamyl transferase Glucose HbA1C Inorganic phosphate Potassium QuantiFERON-TB Gold test Sodium Total CO_2 (measured as bicarbonate) Total creatine kinase Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Serology[b]:	**Drug screen[c]:**	**Hormone panel - females only:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test Alcohol breath test	Follicle-stimulating hormone[b] Serum pregnancy test (human chorionic gonadotropin)[d] Urine pregnancy test[d]
		Other Tests:
		Hepatotoxicity only: International normalized ratio (INR)[e] Estimated glomerular filtration rate(eGFR)[f] Creatine kinase MB fraction[c]

[a] Includes total, direct, and indirect.
[b] Only analyzed at Screening.
[c] Only analyzed at Screening and Check-in.
[d] Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[e] International normalized ratio will be tested if hepatotoxicity is suspected, per guidelines presented in Appendix 7.
[f] Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease equation.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations	7.5	6	45
Serology	3.5	1	3.5
Serum FSH	4	1	4
Serum pregnancy test	4	1	4
AMG 592 pharmacokinetics	4	15	60
Lymphocyte subsets	4	5	20
Biomarker development samples	4	7	28
Anti-AMG 592 and anti-IL-2 Antibodies	4	4	16
Total:			180.5

FSH = follicle-stimulating hormone; IL-2 = interleukin 2

If additional blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: Contraception Requirements

All subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they conceive a child during treatment and for 90 days after the end of study (EOS) visit.

Additional medications given during the study may alter the contraceptive requirements. The Investigator must discuss these contraceptive changes with the subject.

Definitions

Women of Childbearing Potential:

Premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Non-Childbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Requirements

Female Subjects

Female subjects who are of non-childbearing potential will not be required to use contraception.

Female subjects of childbearing potential must be willing to use 2 methods [1 primary (highly effective) and 1 secondary method] of birth control from the time of signing the informed consent form until 90 days after the EOS visit.

Primary (highly effective) methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill associated with inhibition of ovulation (as prescribed) without supplementary iron (ie, Loestrin Fe, Junel Fe, and Lo Loestrin Fe are prohibited)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
    - Bilateral tubal ligation with confirmation of surgical success
    - Regulatory approved method of hysteroscopic bilateral tubal occlusion with confirmation of occlusion of the fallopian tubes
- hormonal implant
- hormonal or non-hormonal intrauterine device (IUD or IUS)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects should refrain from donation of ova from Check-in (Day -1) until 90 days after the EOS visit.

Male Subjects:

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception by female partner from Check-in until 90 days after the EOS visit. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or regulatory approved method of hysteroscopic bilateral tubal occlusion)
- hormonal implant
- hormonal or non-hormonal IUD
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide.

Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the EOS visit.

Sexual Abstinence

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the informed consent form (ICF) until 90 days after the EOS visit.

Same-sex Relationships

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the EOS visit.

Appendix 5: Collection of Pregnancy and Lactation Information

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 90 days after EOS.
- Information will be recorded on the Pregnancy Notification Form (see Figure 3). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 90 days after EOS. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse events or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to the Sponsor as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly), the Investigator will report the event as a serious adverse event.

- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator will be reported to Amgen Global Patient Safety as described in Appendix 1. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 4.5 for details).

Male Subjects with Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 90 days after EOS, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 3) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The Investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- The Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 90 days after the EOS.

- Information will be recorded on the Lactation Notification Form (Figure 4) and submitted to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event.
- Study treatment will be discontinued if the female subject breastfeeds during the study.

With the female subject's signed authorization for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 90 days after discontinuing protocol-required therapies.

Figure 3: Pregnancy Notification Form

AMGEN® **Pregnancy Notification Form**

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20200102/8448873

Study Design: [x] Interventional [ ] Observational (If Observational: [ ] Prospective [ ] Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** [ ] Female [ ] Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? [ ] Yes [ ] No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? [ ] Yes [ ] No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ [ ] Unknown [ ] N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? [ ] Yes [ ] No [ ] Unknown [ ] N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? [ ] Yes [ ] No [ ] Unknown [ ] N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Figure 4: Lactation Notification Form

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: Amgen Protocol Reference Number: 20200102, Covance Study Number: 8448873

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
AMG 592				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
- Notifying the EC of serious adverse events or other significant safety findings as required by EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

An initial sample ICF will be provided for the Investigator (or designee) to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Study Manager to the Investigator. The written ICF is to be prepared in the language(s) of the potential study participant population.

The Investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and the Ethics Committee (EC) or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 21 days from the previous ICF signature date.

Subject Data Protection

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to the Sponsor.

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic case report form (eCRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to the Sponsor, subjects are to be identified by their unique subject identification number, (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to the Sponsor (eg, signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the EC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential information of the Sponsor, Amgen Inc. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written permission from the Sponsor.

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic CRF (eCRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the Investigator, except as described below.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- The contract research organization (CRO) is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify

the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

The policy for publication of data obtained during this study will be documented in the clinical study agreement.

Appendix 7: Hepatotoxicity: Suggested Actions and Follow-up Assessments

Subjects with normal hepatic function at Screening who experience aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3 x upper limit of normal (ULN) or subjects with elevated values before drug exposure who have a 2-fold increase above baseline values (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009) are to undergo clinical assessments and a period of "close observation" until abnormalities return to normal or to the subject's baseline level as described below.

Clinical Assessments and Observation

Assessments that are to be performed during this period include:

- Repeat AST, ALT, alkaline phosphatase, bilirubin (total and direct), and international normalized ratio (INR) within 24 hours
- In cases of total bilirubin (TBL) > 2 x ULN or INR > 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever

- Prior and/or concurrent use of alcohol, recreational drugs, and special diets
- Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms

- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or are considered stable by the Investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential drug-induced liver injury (DILI) event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding electronic case report form (eCRF).

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms

- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis).

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, ie, cases of AST or ALT > 3 x ULN and concurrent TBL > 2 x ULN or INR > 1.5 (for subjects not on anticoagulation therapy) without evidence of alternative cause of the elevations, require the following:

- The event is to be reported to the Sponsor as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate eCRF captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Sponsor.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 1.

Appendix 8: Schedule of Assessments

PROCEDURE	Screening	Check-in		Treatment Period														
		Resident at the Clinical Research Unit																
Study Day	**-28 to -2**	**-1**	**1**	**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**11**	**15**	**22**	**29**	**43[a] (EOS)/ET**
Relative to Dosing (Hours)			**Pre**	**0**	**6**	**12**	**16**	**24**	**48**	**72**	**96**	**120**	**168**	**240**	**336**	**504**	**672**	**1008**
GENERAL AND SAFETY ASSESSMENTS																		
Informed Consent	X																	
In-house Residency[b]		◄							►	◄	- - -	- - -	- - -	►				
Physical Examination[c]	X	X							X					X		X	X	X
Medical History	X	X[d]																
Weight	X																	
Height	X																	
ECG[e]	X	X																
Vital Signs[f]	X	X	X					X	X			X	X	X		X		X
Adverse Events[g]	◄	―	―	―	―	―	―	―	―	―	―	―	―	―	―	―	―	►
Serious Adverse Events[h]	X	◄	―	―	―	―	―	―	―	―	―	―	―	―	―	―	―	►
Concomitant Therapy Review[i]	◄	―	―	―	―	―	―	―	―	―	―	―	―	―	―	―	―	►
LABORATORY ASSESSMENTS																		
Pregnancy Test[j]	X	X																X
Chemistry and Hematology[k]	X	X							X					X		X		X
Serology	X																	
Urinary Drug Screen	X	X																
Alcohol Breath Test	X	X																
Urinalysis	X	X							X					X		X		X
eGFR[l]	X	X																
FSH[m]	X																	
BIOMARKER AND IMMUNOLOGICAL ASSESSMENTS																		
Lymphocyte Subsets		X											X		X	X		X
Biomarker Development Samples		X			X	X							X		X	X		X
Anti-AMG 592 and Anti-IL-2 Antibodies		X													X		X	X
PHARMACOKINETIC ASSESSMENTS																		
AMG 592 Serum PK Collection[n]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
STUDY TREATMENT																		
AMG 592 Administration				X														

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = follicle-stimulating hormone; PE = physical examination; PK = pharmacokinetic

[a] Subjects who test positive at the EOS timepoint for neutralizing antibodies to IL-2 or binding antibodies with potentially antibody-mediated clinical sequelae that are considered potentially related to an anti-AMG 592 antibody response will be asked to return for additional follow-up testing every 3 months until antibodies are no longer detectable or up to 12 months' post administration of AMG 592 (whichever is shorter).

[b] In-house residency from Day -1 through the completion of all assessments on Day 3. Solid line indicates time that subjects are required to stay in the CRU. Dashed line indicates that subjects may stay in the CRU after Day 3 until a maximum of Day 11 if they choose (to reduce travel and accommodation burden on subjects).

[c] Physical examination to include a neurological examination. A full PE will be conducted at Screening. A symptom-directed PE will be conducted on Days -1, 3, 11, 22, 29, and 43/EOS.

[d] Interim medical history only.

[e] Electrocardiogram (ECG) will be single 12-lead ECG, prior to blood draws or invasive procedures.

[f] Supine blood pressure (BP), supine heart rate, respiratory rate, and oral body temperature. Heart rate and BP will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes.

[g] Adverse events will be recorded from initiation of study treatment on Day 1 until the EOS. Any events prior to study drug administration but deemed by the Investigator to be related to study procedures will be reported as adverse events.

[h] Serious adverse events will be recorded from the time the subject signs the informed consent form until the EOS.

[i] Prior and concomitant medication administration will be recorded beginning at informed consent. Also, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) before Day 1 for over-the-counter or prescription medications, and 30 days prior to Check-in for herbal medicines (eg, St. John's wort), vitamins, or supplements will be recorded on the subject's electronic case report form.

[j] Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

[k] Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations.

[l] The eGFR will be calculated using the Modification of Diet in Renal Disease equation.

[m] Performed in females only.

[n] Blood samples for determination of AMG 592 serum concentrations and PK parameters will be collected: Predose; 6, 12, and 16 hours postdose; and on Days 2 (24 hours postdose), 3, 4, 5, 6, 8, 11, 15, 22, 29, and 43 (EOS) following administration of AMG 592 on Day 1. The postdose samples collected on Days 1 and 2 (6, 12, 16, and 24 hour samples) will have a sampling window of ± 30 minutes, postdose samples collected on Days 3 and 4 will have a sampling window of ± 6 hours, postdose samples collected on Days 5 through Day 15 will have a sampling window of ± 1 day, postdose samples taken on Days 22 and 29 will have a sampling window of ± 2 days, and postdose samples taken on Day 43 (EOS) will have a sampling window of ± 4 days. Times of all PK samples will be recorded to the nearest minute.