Title Page

Protocol Title:		**A Randomized, Double-blind, Placebo-controlled Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Multiple Ascending Subcutaneous Doses of AMG 592 in Subjects With Systemic Lupus Erythematosus**
Short Protocol Title:		**Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Immunogenicity** of AMG 592 in Subjects with Systemic Lupus Erythematosus
Protocol Number:		20170103
Investigational Product:		AMG 592
Trade Name:		Not applicable
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EudraCT Number:		2017-002564-40
NCT Number:		NCT03451422
Protocol Date:		

Document Version	**Date**
Original	13 August 2017
Amendment 1	26 July 2018
Amendment 2	12 June 2019
Amendment 3	18 November 2019
Amendment 4	06 February 2020
Superseding Amendment 4	24 February 2020
Amendment 5	**23 April 2020**
Superseding Amendment 5	**25 June 2020**

Version/Date:	**Data Element Standards Version**
	5.0

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Investigator's Agreement:

I have read the attached protocol entitled **A Randomized, Double-blind, Placebo-controlled Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Multiple Ascending Subcutaneous Doses of** AMG 592 in Subjects with Systemic Lupus Erythematosus, dated **25 June 2020**, and agree to abide by all provisions set forth therein.

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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

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: A Randomized, Double-blind, Placebo-controlled Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Multiple Ascending Subcutaneous Doses of AMG 592 in Subjects with Systemic Lupus Erythematosus

Short Protocol Title: Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Immunogenicity of AMG 592 in Subjects with Systemic Lupus Erythematosus

Study Phase: 1b

Indication: Systemic Lupus Erythematosus

Rationale

This is a double-blind, placebo-controlled, multicenter, phase 1b study to evaluate the safety, **tolerability, Pharmacokinetics (PK), Pharmacodynamics (PD), and immunogenicity** of AMG 592 in subjects with systemic lupus erythematosus (SLE). This information will be used to determine the recommended phase **2** dose**(s)**.

Objective(s)/Endpoint(s)

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

Hypotheses

AMG 592 will be safe and well tolerated in subjects with SLE.

Overall Design

This phase 1b study is a double-blind, placebo-controlled, multiple ascending dose (MAD) study to evaluate the safety, tolerability, PK, **immunogenicity,** and PD of AMG 592 in subjects with SLE. Subjects will be treated for a total of 12 weeks after which they will be followed for an additional 6 weeks for safety and additional PK/PD data collection.

Five dosing cohorts are planned for the study. For cohorts 1, 2, and 3, subjects within a dosing-cohort will be randomized in a 5:2 ratio to AMG 592 (n = 5) or placebo (n = 2) as follows: cohort 1 ([redacted] µg [redacted] cohort 2 ([redacted] µg [redacted] and cohort 3 ([redacted] µg [redacted]), in addition to standard of care therapy. For cohorts 4 and 5, subjects within a dosing-cohort will be randomized in a 3:1 ratio to AMG 592 (n = 3) or placebo (n = 1) as follows: cohort 4 ([redacted] µg [redacted] and cohort 5 ([redacted] µg [redacted] in addition to standard of care therapy. Dosing cohorts will enroll sequentially. A Dose Level Review Meeting (DLRM) will convene after the last subject in each cohort completes the week 4 visit. The decision to dose the next cohort will be based on the aggregated review of safety data. After incidents of interest (including selected adverse events or intolerable PD levels) are observed, a Bayesian logistic regression model (BLRM) will be implemented to model these events before each DLRM to aid dosing recommendations. Dose Level Review Meeting members will be responsible for dosing recommendations, which may include escalation to the next planned dose or a new higher dose, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing. Additional dosing cohorts may be added and/or existing cohorts may be expanded based on emerging data. Dose Level Review Meeting members may also consider available aggregated summaries of emerging PK and PD data. Amgen DLRM members may consider safety, PK and PD data from other completed and ongoing phase 1b studies to aid dosing recommendations. Emerging safety, PK, and PD data from ongoing AMG 592 studies may be used to support recommendations to skip dosing cohorts, reduce dosing cohort size or change doses for a given cohort or stop the study entirely.

Number of Subjects

Within each cohort subjects will be randomized to AMG 592 or placebo in a 5:2 ratio (cohorts 1, 2, and 3) or in a 3:1 ratio (cohorts 4 and 5). It is planned that approximately 29 subjects will be randomized, with 21 subjects randomized to AMG 592, and 8 subjects randomized to placebo. The total sample size may exceed 29 subjects and the number of subjects per cohort may exceed the planned cohort size if, following a DLRM recommendation or Amgen decision to evaluate additional doses (or further evaluate currently planned doses), dosing cohorts are added and/or existing cohorts are expanded, or subjects are replaced as per Section 5.2.1. Additional subjects may be

enrolled in each cohort (following originally planned randomization ratio) to enable all screened eligible subjects to participate in the study.

Summary of Subject Eligibility Criteria

Subjects must be adults with SLE according to the Systemic Lupus International Collaborating Clinics (SLICC criteria) or by at least 4 of the 11 criteria of the 1997 American College of Rheumatology (ACR) classification criteria for SLE, with a history of at least one of the following: antinuclear antibody ≥ 1:80; or elevated anti-dsDNA antibodies. Subjects must be on a SLE treatment for ≥ 12 **weeks, may be taking ≤ 3 SLE treatments,** and have a stable dose for ≥ 4 weeks prior to day 1. Subjects must have a prednisone dose ≤ 20 mg daily (or other equivalent OCS) with stable dose ≥ 2 weeks prior to day 1. Subjects must be free of infections and significant concurrent medical conditions and laboratory abnormalities including a negative test for tuberculosis, hepatitis B and C, human immunodeficiency virus, and urine drug and alcohol. Women of childbearing potential must have a negative pregnancy test at screening and baseline and must agree to use a highly effective method of birth control.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

Treatments

AMG 592 and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Both are liquid formulations presented in highly similar glass vials and stored in the same manner. AMG 592 or placebo will be administered by SC injection [redacted].

Five dose cohorts are planned (cohort 1: [redacted] µg [redacted] cohort 2: [redacted] µg [redacted] cohort 3: [redacted] µg [redacted] cohort 4: [redacted] µg [redacted] and cohort 5: [redacted] µg [redacted]

Procedures

Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed. The following procedures will occur per the schedule of activities: medical and medication history, physical examination, physical measures, vital signs, electrocardiograms, prior and concomitant medication assessment, tuberculosis testing, urinalysis, and blood draw for serum chemistry, hematology, hepatitis B and C testing, human immunodeficiency virus testing, PK/PD, anti-AMG 592 antibodies, biomarker development and pharmacogenetics sample. Women of childbearing potential will have pregnancy tests performed at screening and at regular intervals during the study. Safety assessments including adverse events,

serious adverse events, and disease-related events, will be performed throughout the safety follow-up.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1 and Table 2-2.

Statistical Considerations

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

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. **Subject incidence** 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 incidence of disease-related events, and fatal disease-related events, if applicable, will be tabulated by system organ class and preferred term.

The analyses of safety laboratory endpoints will include summary statistics at selected time points by treatment group. Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated.

For a full description of statistical analysis methods, please refer to Section 10.

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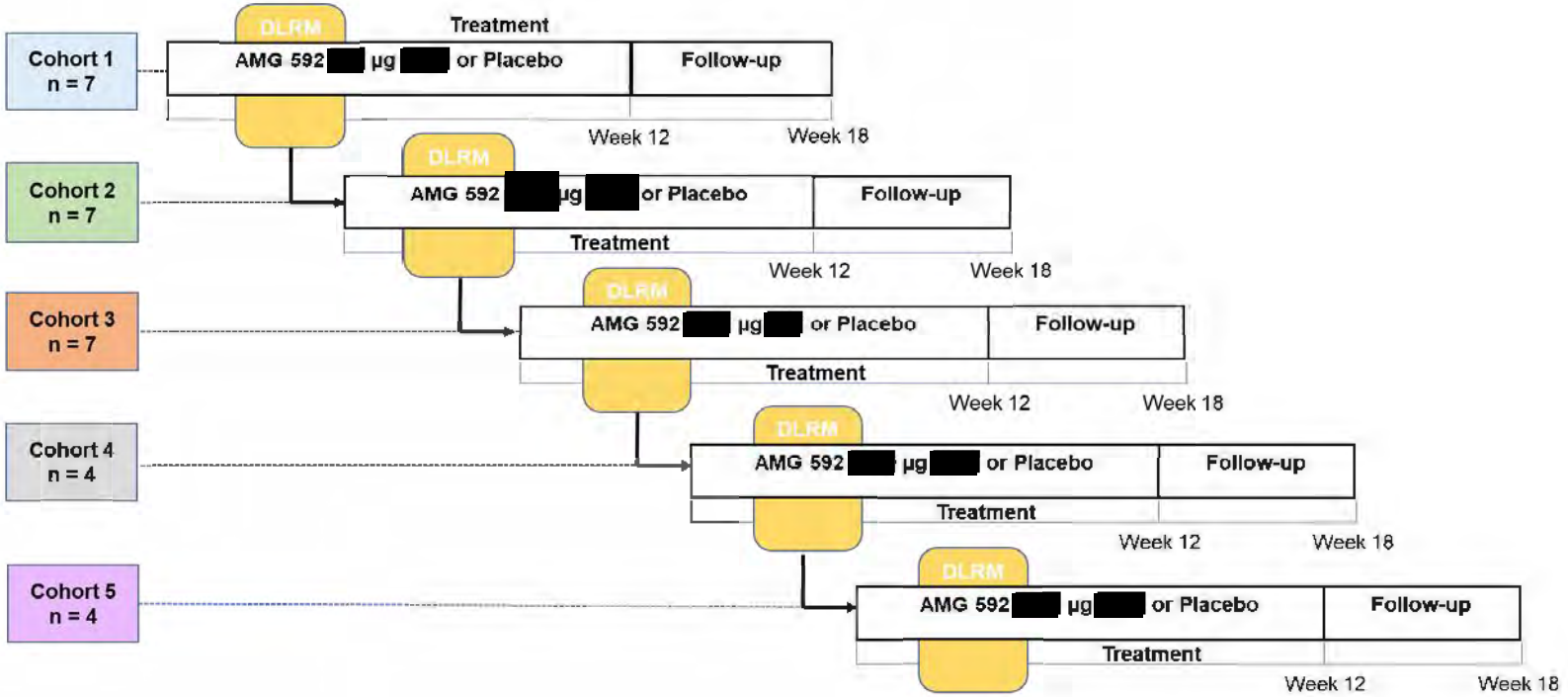
2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



DLRM = Dose Level Review Meeting; [redacted].

Each **of** cohorts 1, 2, and 3 will **plan to enroll** 5 AMG 592: 2 placebo subjects and cohorts 4 and 5 will **plan to enroll** 3 AMG 592: 1 placebo **subject**. Doses and size of treatment cohorts may change as determined by emerging safety data, Bayesian logistic regression model (BLRM), and pharmacokinetic/pharmacodynamic modeling.

DLRM: 4 weeks after the last subject in cohort enrolled

Treatment Period: 12 weeks

2.2 Schedule of Activities

Table 2-1. Schedule of Activities: Screening and Treatment Period

			Treatment Period																												
Study week											1		2	3	4	5	6	7	8	9	10	11	12								
Study day			1[m]					2[m]	3[m]	4[m]	8	11[m]	15	22	29	36	43	50	57	64	71	78	85[m]					86[m]	87[m]	88[m]	
Hours post dose	**Screening (- 28)**	**Day -1**	**Pre-dose**	**0**	**0.25 -2.0**	**6**	**12**	**24**	**48**	**72**													**Pre-dose (ET)[k]**	**0**	**0.25 -2.0**	**6**	**12**	**24**	**48**	**72**	
GENERAL AND SAFETY ASSESSMENTS																															
Informed consent	X																														
Eligibility	X	X	X																												
Demographics	X																														
Physical examination	X														X				X				X								
Height	X																														
Weight	X		X																				X								
Medical history	X	X																													
Substance use	X	X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X	
Strenuous Activity Assessment	X	X													X				X				X								
ECG[a]	X	X															X											X			
Vital signs	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chest X-ray[b]	X																														
Adverse events[c]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	
Serious adverse events[c]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	
Disease-related events[c]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	
Prior therapies review	X	X	X																												
Concomitant medication review					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X	

Footnotes are defined on the last page of the table

Table 2-1. Schedule of Activities: Screening and Treatment Period

	Screening (-28)	Day -1	Treatment Period																													
Study week											1		2	3	4	5	6	7	8	9	10	11	12									
Study day			1[m]					2[m]	3[m]	4[m]	8	11[m]	15	22	29	36	43	50	57	64	71	78	85[m]					86[m]	87[m]	88[m]			
Hours post dose			**Pre-dose**	**0**	**0.25 -2.0**	**6**	**12**	**24**	**48**	**72**													**Pre-dose (ET[k])**	**0**	**0.25 -2.0**	**6**	**12**	**24**	**48**	**72**			
LABORATORY ASSESSMENTS																																
Serum and/or urine pregnancy test[d]	X	X													X				X				X									
Tuberculosis test[e]	X																															
Urine drug/alcohol screen	X																															
HIV, Hepatitis B and C[f]	X																															
C3 and C4 complement[f]		X									X				X				X				X									
Anti-dsDNA	X	X									X				X				X				X									
Antinuclear antibody[l]	X	X																														
Hematology[f]	X	X						X					X		X		X		X		X		X									
Chemistry[f]	X	X													X				X				X									
FSH[g]	X																															
Urinalysis		X													X				X				X									
PBMC[f]			X								X				X				X				X									
EFFICACY ASSESSMENTS																																
SLEDAI-2K		X													X				X				X									
PHARMACODYNAMIC ASSESSMENTS																																
Lymphocyte subsets[h]			X					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X									
PHARMACOKINETICS AND ANTIBODIES																																
Pharmacokinetic samples[h]			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X		
Anti-AMG 592 antibody[f]			X										X		X				X				X									
BIOMARKER AND PHARMACOGENETICS																																
Biomarker development sample[f]			X					X		X	X		X		X				X				X									
Pharmacogenetics sample[i]			X																													

Footnotes are defined on the next page of the table

Table 2-1. Schedule of Activities: Screening and Treatment Period

	Screening (-28)	Day -1	Treatment Period																														
Study week											1		2	3	4	5	6	7	8	9	10	11	12										
Study day			1[m]					2[m]	3[m]	4[m]	8	11[m]	15	22	29	36	43	50	57	64	71	78	85[m]					86[m]	87[m]	88[m]				
Hours post dose			**Pre-dose**	**0**	**0.25 -2.0**	**6**	**12**	**24**	**48**	**72**													**Pre-dose (ET)[k]**	**0**	**0.25 -2.0**	**6**	**12**	**24**	**48**	**72**				
INVESTIGATIONAL PRODUCT ADMINISTRATION																																	
Investigational product QW[j]				X							X		X	X	X	X	X	X	X	X	X	X		X								
Investigational product Q2W[j]				X									X		X		X		X		X			X								

ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; QW = every week; Q2W = every other week; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

[a] single ECG will be collected at screening and after day -1. At day -1 (baseline) a triplicate ECG will be collected. See Section 9.2.3.3.

[b] Only for subjects with a positive tuberculosis test (ie, positive purified protein derivative [PPD] or a positive or indeterminate Quantiferon)

[c] For subjects who complete the study at week 18, the visit includes all required safety follow-up data collection (see Table 2-2). For subjects who terminate the study early (ie, prior to completing the week 18 visit), the safety follow-up visit 6 weeks (± 3 days) after the last dose of investigational product will be a visit to collect adverse events, serious adverse events, disease related events, ECG, hematology and concomitant medications only.

[d] For women of childbearing potential, serum pregnancy test is required at screening. All other pregnancy tests are urine.

[e] Either a PPD or Quantiferon test will be done during screening.

[f] Blood samples must be collected prior to administration of investigational product with the exception of the 6 and 12 hour PK samples on days 1 and 85.

[g] Can be done as a part of the clinical chemistry

[h] Pharmacokinetic and lymphocyte subset blood samples should be collected at the exact nominal time point as noted above (see hour postdose column). If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. For samples without exact nominal time point (ie, days 8 to 78), PK samples must be collected prior to administration of investigational product, where appropriate. Pharmacokinetic and lymphocyte subset samples not collected at exact nominal time point will not be considered protocol deviations.

[i] DNA will be extracted only in subjects who provide additional consent for pharmacogenetics testing.

[j] Investigational product must be administered within ± 12 hours from the scheduled time point up until week 4. After week 4, investigational product must be administered within ± 1 day of the scheduled time point. If that window is missed, that dose will not be administered, and the next dose will be administered at the next scheduled dosing date. Subjects will remain at the site for at least 1 hour following the first and second doses of investigational product and for at least 30 minutes following subsequent doses.

[k] Subjects who withdraw from investigational product early will complete an early termination visit that includes the week 12 (predose) assessments.

[l] To be collected at screening but not required for eligibility unless subject has no documented prior history of antinuclear antibody (ANA) ≥ 1:80 or elevated anti-dsDNA.

[m] For description of home healthcare services available, see Section 9.2.3.4.

Table 2-2. Schedule of Activities Follow-up

	Follow-up			
Study week	**13**	**14**	**16**	**18/SFU/EOS[a]**
Study day	**92**	**99**	**113**	**127**
GENERAL AND SAFETY ASSESSMENTS				
Weight				X
Vital signs	X	X	X	X
ECG				X
Adverse events	X	X	X	X[a]
Serious adverse events	X	X	X	X[a]
Disease-related events	X	X	X	X[a]
Concomitant medications review	X	X	X	X[a]
LABORATORY ASSESSMENTS				
Urine pregnancy test			X	X
Anti-dsDNA and C3 and C4 complement				X
Hematology		X	X	X
Chemistry				X
PBMC				X
PHARMACODYNAMIC ASSESSMENTS				
Lymphocyte subsets	X	X	X	X
PHARMACOKINETICS AND ANTIBODIES				
Pharmacokinetic samples	X	X	X	X
Anti-AMG 592 antibody				X
BIOMARKER				
Biomarker development sample				X

ECG = electrocardiogram; EOS = end of study for individual subject; PBMC = peripheral blood mononuclear cell; SFU = Safety follow-up

[a] For subjects who complete the study at week 18, the visit includes all required safety follow up data collection. For subjects who terminate the study early (ie, prior to completing the week 18 visit), the safety follow-up visit 6 weeks (± 3 days) after the last dose of investigational product will be a visit to collect adverse events, serious adverse events, disease related events, ECG, **hematology,** and concomitant medications only

3. Introduction

3.1 Study Rationale

This phase 1b study is a double-blind, placebo controlled, multiple ascending dose (MAD) study to evaluate the safety and tolerability of AMG 592 in subjects with systemic lupus erythematosus (SLE) and to determine the recommended phase 2 dose**(s)**.

3.2 Background

3.2.1 Disease

Systemic lupus erythematosus is a multisystem autoimmune disease of unknown cause with diverse clinical manifestations that disproportionately affects minorities (eg, in the United States, blacks and Hispanics) and women of childbearing potential (Rhaman and Isenberg, 2008; Kotzin, 1996). In the United States (US), moderate to severe SLE is estimated to affect one-third of the more than the 250 000 patients diagnosed with lupus. The progression of Systemic Lupus Erythematosus (SLE) may vary from mild episodes to severe, even fatal outcomes with symptoms varying widely in individuals over time and characterized by periods of remission and flare. Systemic lupus erythematosus can affect the skin (rash), musculoskeletal system (arthritis, bone tissue death), nervous system (seizures, psychosis), lungs (pleuritis, pneumonitis), and the blood (venous or arterial clots, anemia). In addition, approximately 65% of patients will develop lupus nephritis, which is an inflammation of the kidney that can range from mild glomerulonephritis to severe diffuse proliferative glomerulonephritis (Adams et al, 2006).

Currently, corticosteroids, immunosuppressants, and cytotoxic agents are frequently used to control active disease, but significant need exists for more effective therapies with fewer short- and long-term toxicities. Although the clinical heterogeneity of SLE presents challenges in the diagnosis, antibodies to nuclear components represent almost a prerequisite for the disease. The presence of class-switched immunoglobulin G (IgG) autoantibodies implicate immune dysregulation as a driving force for disease pathogenesis, with T cells appearing to play a role in the development of autoantibody production by B cells.

3.2.1.1 Interleukin 2 and T Regulatory Cells in Systemic Lupus Erythematous

T regulatory cells (Tregs) are a subset of T cells that maintain self- tolerance by suppressing the activation and expansion of autoreactive lymphocytes. Defects in Treg numbers or function have been described in SLE patients and are thought to contribute

to SLE pathogenesis (Zhang et al, 2008; Bonelly et al, 2009; Myara et al, 2005; Suen et al 2008; von Spee-Mayer **et al** 2015). Interleukin-2 (IL-2), a multi-functional cytokine produced predominantly by activated cluster of differentiation 4+ (CD4+) T cells, is a key growth factor for Tregs and is essential for Treg maintenance, survival and metabolism (Malek and Castro, 2010; Boyman and Sprent, 2012). Impaired IL-2 production has been reported in patients with SLE (Linker-Israeli et al, 1983; Alcocer-Varela and Alarcon Segovia, 1982; von Spee-Mayer et al, 2015). Moreover, reduced levels of circulating IL-2 have been associated with Treg dysfunction in SLE patients (Lieberman and Tsokos, 2010; von Spee-Mayer et al, 2015). These data suggest that immune homeostasis in SLE patients may be restored by correction of Treg dysfunction and numerical deficiency through treatment with low dose IL-2.

3.2.1.2 Low Dose Interleukin 2 in Inflammatory Disease

Low dose IL-2 (aldesleukin) has been shown to increase Treg numbers in multiple inflammatory diseases such as Type 1 Diabetes (Yu et al, 2015), chronic graft versus host disease (GVHD) (Koreth et al, 2011), hepatitis c virus induced vasculitis (Sadoun et al, 2011) and alopecia areata (Castela et al, 2014); as well as to correct defects in Treg function in SLE (von Spee-Mayer et al, 2015), Type 1 Diabetes (Long et al, 2010; Long et al, 2012) and GVHD (Matsuoka et al, 2013). Genetic variants of the IL 2 receptor have been associated with the severity of rheumatoid arthritis (RA) joint destruction and persistence (van Steenbergen et al, 2015).

The therapeutic efficacy of low dose IL-2 has also been studied in chronic GVHD (cGVHD) (Koreth et al, 2011; Koreth et al, 2016), hepatitis C induced vasculitis (Sadoun et al, 2011), and alopecia areata (Castela et al, 2014). The clinical response to low dose IL-2 has been promising in these small early phase studies in multiple diverse inflammatory conditions, with efficacy reported in all indications. In all of these conditions the overall safety and tolerability profile of low-dose IL-2 has been acceptable with mild to moderate constitutional symptoms associated with higher levels of exposure. However, the therapeutic window between adequate Treg enrichment and stimulation of effector cells is narrow and may limit achievement of optimal Treg expansion. For instance, in a recent phase 1b clinical trial of cGVHD (ClinicalTrials.gov NCT00529035), aldesleukin, a human recombinant IL-2, given at the dose of 3×10^6 IU/m^2 daily induced persistent National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grade 1 constitutional symptoms (fever, malaise, and arthralgia) necessitating a 50% dose reduction (Koreth et al, 2011). In addition,

aldesleukin can activate pro-inflammatory/effector lymphocytes such as CD4+ T effector cells (Teff) and natural killer (NK) cells, which may compromise efficacy and safety. These data suggest the potential for a therapeutic agent with greater Treg selectivity and a prolonged PD effect compared with recombinant IL-2.

3.2.1.3 Clinical Experience With Low Dose IL-2 in Systemic Lupus Erythematosus

Treatment with low dose IL-2 has been associated with clinical efficacy in 2 small clinical trials. In one recently reported study of 12 patients with moderate to severe SLE (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] score ≥ 6 despite treatment with 2 different immunosuppressive therapies), 10/12 subjects (83.3%) achieved a reduction in SELENA SLEDAI score and 8/12 (66.7%) achieved a clinical response after receiving four 5-day cycles of low dose IL-2 therapy separated by washout periods of 9 and 16 days. Clinical responses included complete resolution of SLE manifestations including rash, arthralgias, myositis and alopecia. Complement levels increased but no change in anti-double stranded DNA (anti-dsDNA) antibodies was observed. Regulatory T cells numbers increased in all treated subjects (Humrich et al, 2016; Humrich et al, 2015). In a second study of 38 SLE patients who completed three 2-week cycles of low dose IL-2 over 12 weeks, 34/38 subjects (89.5%) achieved a Systemic Lupus Erythematosus Responder Index 4 (SRI-4) response at the end of 12 weeks, with concomitant decreases in anti-dsDNA antibodies and increase in complement levels. Regulatory T cells numbers increased in most treated subjects (He et al, 2016). In both studies low dose IL-2 was generally well- tolerated, though constitutional symptoms (eg, fever, myalgias, arthralgias, flu-like symptoms) were reported at the higher dose levels. Overall these studies provide compelling support for further investigation of low dose IL-2 for the treatment of SLE.

3.2.2 Amgen Investigational Product Background: AMG 592

AMG 592 is an Fc IL-2 mutein fusion protein with increased Treg selectivity compared to recombinant IL-2, which has been developed to preferentially expand Tregs in subjects with inflammatory diseases (refer to the Investigator's Brochure for more details). Interleukin-2 is a key growth factor for Tregs and is essential for Treg development, homeostasis and function. At low doses IL-2 binds preferentially to the α-subunit (CD25) of the high-affinity IL-2 receptor which is expressed constitutively by Tregs and is absent on naive T-cells and unactivated T memory cells. This results in selective activation of Tregs. However, at higher doses IL-2 also activates other immune cells such as CD4+ and CD8+ Teff, NK cells and natural killer T cells (NKT) cells via the dimeric low affinity

IL-2 receptor. Compared with aldesleukin, AMG 592 exhibits greatly improved selectivity for Tregs over Teff and NK cells both in vitro and in vivo, potentially resulting in an improved therapeutic margin. In addition, the Fc domain of AMG 592 provides a prolonged half-life compared with aldesleukin, thus reducing dosing frequency to maintain Treg enrichment.

3.2.2.1 Toxicology

[redacted]

3.2.2.2 Human Exposure

[redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of AMG 592 is provided in the Investigator's Brochure.

3.3 Risk Assessment

Repeated SC doses of up to [redacted] µg administered [redacted] **and** [redacted] have been studied for up to **12 weeks** in subjects with rheumatoid arthritis and SLE. **In addition, repeated SC doses of up to** [redacted] **µg** [redacted] **for up to 52 weeks have been studied in subjects with cGVHD.** The most **frequent** adverse event was mild (grade 1 or 2) painless erythema at or near the injection site, sometimes accompanied by pruritus, that was self-resolving. Two serious hypersensitivity reactions to AMG 592 have been reported, though none occurred in the current study. No clinically significant therapeutic related abnormalities in electrocardiograms (ECGs), hematological or biochemical laboratory investigations, or vital signs have been reported. No adverse events greater than grade 2 assessed as related to AMG 592 nor any deaths have occurred in the phase 1b part of the current study in SLE patients. More detailed information about the known and expected risks

and reasonably expected adverse events associated with AMG 592 may be found in the Investigator's Brochure.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

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

4.2 Hypotheses

AMG 592 will be safe and well tolerated in subjects with SLE.

5. Study Design

5.1 Overall Design

This phase 1b study is a double-blind, placebo-controlled, **multiple ascending dose (**MAD**)** study to evaluate the safety, tolerability, PK, **immunogenicity**, and PD of AMG 592 in subjects with SLE. Subjects within a dosing cohort will be randomized to AMG 592 or placebo in a 5:2 ratio (cohorts 1, 2, and, 3) or in a 3:1 ratio (cohorts 4 and 5) in addition to standard of care therapy as shown in [redacted] AMG 592 or placebo will be administered either [redacted] by SC injection. Dosing cohorts will enroll sequentially.

[redacted]

The decision to dose-escalate will be based on the blinded review of safety data during the dose level review meeting(s) (DLRM). The DLRM team will include representatives from Amgen's AMG 592 Early Development Team (Amgen Medical Monitor, Amgen Global Safety Officer, Clinical Study Manager, and other team members, as appropriate) and the site investigator(s). The DLRM members will be responsible for dosing recommendations, which may include escalation to the next planned dose or a new higher dose, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing. For further details on the DLRM see Appendix 3.

After the last subject enrolled in each cohort completes the week 4 visit, a DLRM will convene to determine the acceptability of dose escalation. The recommendation to dose the next cohort will be based on the aggregated review of safety data as well as other information as described below. After incidents of interest (including selected adverse events or intolerable PD levels) are observed, a Bayesian logistic regression model (BLRM) (Bailey et al, 2009; Neuenschwander et al, 2008) will be implemented to model these events before each DLRM to aid dosing decisions. Dose level review meeting members may also consider available aggregated summaries of emerging PK

and PD data. Amgen DLRM members may consider safety, PK and PD data from other completed and ongoing phase 1b studies to aid dosing recommendations including skipping dosing cohorts, reducing dosing cohort size or changing doses for a given cohort or stopping the phase 1b portion of the study entirely. If emerging data from other studies is used in support of dosing recommendations, a dose will only be declared tolerable if it is supported by safety from at least 5 subjects at or above this dose level across all phase 1b studies.

Additional dosing cohorts may be added and/or existing cohorts may be expanded. These cohorts may be used to explore alternate dosing levels and/or dosing schedules or add additional subjects at previously given dose levels. A DLRM is required for escalation to higher doses but not for allocation of additional subjects to doses equivalent to or lower than previously given that have been deemed tolerable.

Subjects will be treated for a total of 12 weeks after which they will complete a 6-week follow-up period until week 18 for collection of additional safety, PK and PD data as described in the Schedule of Activities (Table 2-2). In the event that a subject terminates the study early (ie, prior to week 18), a safety follow-up visit will be completed (6 weeks [± 3 days]) after the last dose of investigational product for collection of adverse events, serious adverse events, disease related events, ECG, hematology and concomitant medications only.

Home Healthcare Services

The investigator may utilize a qualified home healthcare service provider approved by the sponsor to conduct the procedures (described in Section 9.2.3.4) required during study visits, subject to the investigator's direction. Home healthcare services will not be used for investigational product administration. Home healthcare staff must be included on the study delegation log (authorized by the investigator) before any study-related tasks to be conducted by each home healthcare provider are started.

In addition, study-specific training including requirements for recording source documentation for the home healthcare provider, must be completed before they conduct any study-related tasks.

If ordered by the principal investigator (PI) or authorized physician, the subject will be visited by a qualified home healthcare service provider at designated study visits as specified in Section 9.2.3.4.

Following home healthcare visit, this information will be documented on the home health care services visit worksheet and forwarded to the investigator.

A comprehensive list of all home healthcare services, as well as mandatory procedural and data collection requirements, will be separately provided in a home health care manual.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Subjects will be randomized to **receive** AMG 592 or placebo in a 5:2 ratio (cohorts 1, 2, and 3) or in a 3:1 ratio (cohorts 4 and 5). Sufficient subjects will be randomized to yield approximately 29 subjects (approximately 21 randomized to AMG 592 and 8 randomized to placebo; see Section 5.2.1). The total sample size may exceed 29 subjects and the number of subjects per cohort may exceed the planned cohort size if, following a DLRM recommendation or Amgen decision to evaluate additional doses or further evaluate currently planned doses, dosing cohorts are added and/or existing cohorts are expanded, or if subjects are replaced as per Section 5.2.1. Additional subjects may be enrolled in each cohort (following originally planned randomization ratio) to enable all screened eligible subjects to participate in the study.

Subjects in this clinical investigation shall be referred to as “subjects.” For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects who have been randomized but discontinue investigational medicinal product before completing the week 4 visit may be replaced.

5.2.2 Number of Sites

Approximately 20 sites in North America and Europe will participate in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, safety follow-up), as applicable.

5.3.2 Study Duration for Subjects

The study will consist of up to a 28-day screening period, a 12-week treatment period and a 6-week follow up. The maximum duration of trial participation for an individual subject will be 22 weeks.

5.4 Justification for Investigational Product Dose

[redacted]

[redacted]

[redacted]

5.5 Patient Input on Study Design

Patient input was not obtained for design of this study.

6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log will be completed and updated via an Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during screening and day -1.
Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures.

102 Age ≥ 18 years to ≤ 70 years at screening.

103 Fulfills diagnostic criteria for SLE according to the Systemic Lupus International Collaborating Clinics (SLICC) criteria or by at least 4 of the 11 criteria of the 1997 American College of Rheumatology (ACR) classification criteria for SLE, with a history of at least one of the following:

- Antinuclear antibody ≥ 1:80; or
- Elevated anti-dsDNA antibodies

104 Removed

105 Removed

106 Removed

107 May be taking ≤ 3 systemic SLE treatments and the dose must be stable for ≥ 4 weeks prior to day 1.

108 Prednisone dose ≤ 20 mg daily (or other equivalent oral corticosteroid) with stable dose ≥ 2 weeks prior to day 1

109 Normal or clinically acceptable ECG values (12-lead reporting ventricular rate and PR, QRS, QT and QTc interval) at screening and baseline based on opinion of the investigator.

110 Immunizations (tetanus, diphtheria, pertussis [Td/Tdap]), seasonal influenza (during flu season), and pneumococcal (polysaccharide) vaccinations] up to date per local standards as determined by the investigator.

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply.

Disease Related

201 History of lupus nephritis requiring induction therapy and/or lupus cerebritis ≤ 1 year prior to screening.

202 Removed

Other Medical Conditions

203 Diagnosis of inflammatory joint or skin disease other than SLE which would interfere with SLE disease assessment based on investigator judgement.

204 Diagnosis of fibromyalgia which would interfere with SLE assessment according to the investigator.

205 Prosthetic joint infection within 3 years of screening or native joint infection within 1 year prior to screening.

206 Active infection (including chronic or localized infections) for which anti-infectives were indicated within 4 weeks prior to day 1 OR presence of serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to day 1.

207 Known history of active tuberculosis

208 Positive test for tuberculosis during screening defined as either:

- positive purified protein derivative (PPD) (≥ 5 mm of induration at 48 to 72 hours after test is placed) OR positive Quantiferon test
    - a positive PPD and a history of Bacillus Calmette-Guérin vaccination are allowed with a negative Quantiferon test and negative chest X-ray.
    - a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or a positive or indeterminate Quantiferon test are allowed if they have ALL of the following at screening:
        - no symptoms per tuberculosis worksheet provided by Amgen
        - documented history of a completed course of adequate prophylaxis (completed treatment for latent tuberculosis per local standard of care prior to the start of investigational product)

- no known exposure to a case of active tuberculosis after most recent prophylaxis
- negative chest X-ray.

209 Positive for hepatitis B surface antigen, hepatitis B core antibody (confirmed by hepatitis B DNA polymerase chain reaction [PCR] test) or detectable hepatitis C virus RNA by PCR (screening is generally done by hepatitis C antibody [HepCAb], followed by hepatitis C virus RNA by PCR if HepCAb is positive). A history of hepatitis B vaccination without history of hepatitis B is allowed.

210 Positive for Human Immunodeficiency Virus (HIV) at screening, or known to be HIV positive.

211 Presence of one or more significant concurrent medical conditions per investigator judgment, including but not limited to the following:

- poorly controlled diabetes or hypertension
- chronic kidney disease stage IIIb, IV, or V
- symptomatic heart failure (New York Heart Association class II, III, or IV)
- myocardial infarction or unstable angina pectoris within the past 12 months prior to randomization
- severe chronic pulmonary disease (eg, requiring oxygen therapy)
- multiple sclerosis or any other demyelinating disease
- major chronic inflammatory disease or connective tissue disease other than SLE (eg, RA).

212 Malignancy except non-melanoma skin cancers, cervical, or breast ductal carcinoma in situ within 5 years of screening.

213 Subjects with a urine test positive for illicit drugs or alcohol at the screening visit. Prescription medications detected by the drug test are allowed if they are being taken under the direction of a physician.

214 History of alcohol or substance abuse within 6 months of screening.

215 Current smoker, and/or use of any nicotine or tobacco containing products within the last 6 months prior to day 1. These types of products include but are not limited to: snuff, chewing tobacco, cigars, cigarettes, electronic cigarettes, pipes, or nicotine patches.

216 Subject unwilling to limit alcohol consumption to ≤ 1 drink of alcohol per day and ≤ 3 drinks per week for the duration of the study, where a drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits.

Prior/Concomitant Therapy

217 Currently receiving or had treatment with: cyclophosphamide, chlorambucil, nitrogen mustard, or any other alkylating agent ≤ 6 months prior to day 1 OR oral calcineurin inhibitors (eg, cyclosporine, tacrolimus, and sirolimus) ≤ 4 weeks prior to day 1.

218 Current or previous treatment for SLE with a biologic agent as follows: rituximab < 6 months prior to day 1, belimumab < 3 months prior to day 1, abatacept < 8 weeks prior to day 1.

219 Currently receiving or had treatment with T cell depleting agents (eg, antithymocyte globulin, Campath) or recombinant IL-2 (eg, Proleukin).

220 Subjects who have received intra-articular or systemic corticosteroid injections within 4 weeks prior to day 1 or topical steroids within 2 weeks prior to day 1.

221 Administration of herbal supplements, vitamins, or nutritional supplements within 30 days prior to the first dose of investigational product, and continuing use, if applicable, will be reviewed by the Investigator and the Amgen Medical Monitor to determine acceptability. Written documentation of this review and Amgen acknowledgment is required for subject participation.

Prior/Concurrent Clinical Study Experience

222 Currently receiving treatment in another investigational device or drug study, or less than 30 days at day 1 since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

223 Subject previously enrolled in this study may not be re-enrolled *unless* they fulfill the following criteria:

- Have completed the study previously without any adverse events deemed related to study drug.
- Have received the last dose of AMG 592/placebo > 6 months prior to the screening visit.
- Must not have tested positive for neutralizing antibodies against AMG 592 at any time.

Diagnostic Assessments

224 Presence of laboratory abnormalities at screening including the following:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN).
- Serum total bilirubin (TBL) $\geq$ 1.5 mg/dL ($\geq$ 26 μmol/L)
- Hemoglobin < 9.0 g/dL (< 90 g/L)
- Platelet count < 100,000/mm^3 (100 x 10^9/L)
- White blood cell count < 2,000 cells/mm^3 (2.0 x 10^9/L)
- Absolute neutrophil count (ANC) < 1,000/mm^3 (1.0 x 10^9/L)
- Calculated glomerular filtration rate of $\leq$ 50 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula.

225 Any other laboratory abnormality, which, in the opinion of the investigator, poses a safety risk, will prevent the subject from completing the study, will interfere with the interpretation of the study results, or might cause the study to be detrimental to the subject.

Other Exclusions

226 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 6 weeks after the last dose of investigational product.

227 Females of child-bearing potential with a positive pregnancy test (assessed by a serum pregnancy test at screening and a urine pregnancy test at baseline).

228 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 6 weeks after the last dose of investigational product. Refer to Appendix 5 for additional contraceptive information.

229 Subject has known sensitivity to any of the products or components to be administered during dosing.

230 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.

231 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

6.3 Lifestyle Restrictions

6.3.1 Alcohol and Tobacco

At screening and throughout the duration of the study, subjects should not consume > 1 drink of alcohol per day and no more than 3 drinks per week, where a drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits.

Subjects must abstain from alcohol consumption within 48 hours prior to each visit (including screening).

Subjects must not use any nicotine or tobacco containing products throughout the study. These types of products include but are not limited to: snuff, chewing tobacco, cigars, cigarettes, pipes, electronic cigarettes, or nicotine patches.

6.3.2 Activity

Subjects will abstain from strenuous exercise (eg, running, weight lifting for greater than 1 hour) for 72 hours before each blood collection for clinical laboratory tests.

6.4 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information, if applicable (see Appendix 3).

The subject must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IRT. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study. In the case of a subject re-enrolling to a new cohort, a new subject identification number will be assigned.

6.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. 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.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened (Section 9.1.1).

7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) 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 investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Section 7.1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

7.1.1.1 Amgen Investigational Product: AMG 592

AMG 592 and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

Both are liquid formulations presented in highly similar glass vials and stored in the same manner. An IPIM containing detailed information regarding the storage, preparation, and administration of investigational product will be provided separately.

7.1.1.1.1 Dosage Administration and Schedule

AMG 592 or placebo will be administered by SC injection [redacted] starting on Day 1. The following dose cohorts are planned:

- Cohort 1: [redacted] µg [redacted] or placebo
- Cohort 2: [redacted] µg [redacted] or placebo
- Cohort 3: [redacted] µg [redacted] or placebo
- Cohort 4: [redacted] µg [redacted] or placebo
- Cohort 5: [redacted] µg [redacted] or placebo

Investigational product will be administered by SC injection in the abdomen, thigh or upper arm by authorized site personnel. A physician must be available at the time of investigational product administration.

The dose of investigational product must be given within ± 12 hours of the specified time point up until week 4 (see Schedule of Activities, Table 2-1). After week 4, doses of investigational product must be given within ± 1 day of the scheduled time point (see Schedule of Activities, Table 2-1). If that window is missed, that dose will not be administered, and the next dose will be administered at the next scheduled dosing date.

Subjects will remain at the site for at least 1 hour following the first and second doses of investigational product and for at least 30 minutes following subsequent doses.

The amount of investigational product used in preparation, total volume of preparation, quantity administered, start date, start time, and box number of AMG 592/placebo are to be recorded on each subject's CRF.

7.1.2 Non-investigational Products

There are no therapies designated as non-investigational products in the study.

7.1.3 Medical Devices

There are no investigational medical device(s) 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 Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

7.1.4 Other Protocol-required Therapies

There are no other protocol-required therapies.

7.1.5 Other Treatment Procedures

There are no other treatment procedures.

7.1.6 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 Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Amgen will collect product complaints in this study for AMG 592.

Any product complaint(s) associated with an investigational product(s), non-investigational product(s), device(s), or combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following medications are not allowed at any time during the study:

- investigational therapies or commercially available biologic agents
- cytotoxic agents including: chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents
- live vaccines
- systemic or topical calcineurin inhibitors (eg, tacrolimus, cyclosporine, etc.)

- T cell depleting agents (eg, antithymocyte globulin, Campath)
- recombinant IL-2 (eg, Proleukin)
- Topical, intra-articular, intramuscular, or intravenous corticosteroids, including adrenocorticotropic hormone
- Intra-articular hyaluronic acid injections

Herbal supplements, vitamins, or nutritional supplements approved by the Amgen Medical Monitor will be allowed.

7.2 Method of Treatment Assignment

Subjects will be randomized to receive AMG 592 or placebo in a 5:2 ratio (cohorts 1, 2, and 3) or in a 3:1 ratio (cohorts 4 and 5) via IRT.

Assignment to the treatment arms will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study. Each randomized subject will receive a single, unique randomization number via **IRT** at randomization. The randomization date is to be documented in the subject's medical record as registered in the **IRT**.

7.3 Blinding

The study is double-blind. Treatment assignment will be blinded to all subjects and site personnel as described below.

7.3.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded when knowledge of the treatment is essential for further clinical management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The Amgen Trial Manager must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition. In this case, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

7.3.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

The Amgen early development lead will be unblinded and will monitor the study on an ongoing basis. Other Amgen staff and their designees involved in the study will not be blinded, but will be given access to the unblinding or potentially unblinding information only when there is a need to use the information for analysis, discussion and internal decision-making, in particular, when concerning safety issues. Access to treatment assignments and other restricted data are described in Amgen standard documents. Unblinded individuals will ensure the keeping of the blind. Unblinding and potentially unblinding information should not be distributed to the investigators or subjects prior to a study cohort being formally unblinded.

7.4 Dose Modification

7.4.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

7.4.1.1 Dose Level Review Meetings

After all subjects within a cohort have had the opportunity to complete the week 4 visit, a DLRM will be held to review data and make dose escalation/de-escalation decisions (see Appendix 3).

7.4.1.2 Dose Cohort Stopping Rules

The following dose cohort stopping rules will be used the study. Dosing will be stopped or modified as shown in Table 7-1.

Table 7-1. Dose Cohort Stopping Rules

Scenario	Action
Any occurrence of a CTCAE version 4.03 Grade 3 suspected adverse event deemed related to investigational product drug reaction of the same system organ class (eg, hepatobiliary, cardiovascular) observed in ≥ 2 or more subjects in a single dosing the same cohort.	Stop dosing and convene DLRM (if event occurs outside the regularly scheduled DLRM) Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Consider unblinding, as appropriate[a]. Based on the DLRM members' majority vote, one of the following recommendations may be made: • stop enrollment of the cohort (if applicable) • resume enrollment of the cohort as planned • expand the cohort at the same dose • enrollment of the study may continue at a lower dose Based on the DLRM members' unanimous vote one of the following recommendations may be made: • escalate to an intermediate dose (a dose lower than the next planned dose) • escalate to the next planned dose
Any occurrence of a CTCAE version 4.03 ≥ Grade 4 or greater suspected adverse drug reaction	Stop dosing additional subjects in the cohort and convene DLRM (if the event occurs outside the regularly scheduled DLRM). Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Consider unblinding to determine relatedness to investigational product[a]. If the adverse event is determined by a majority vote of the DLRM members to be related to the study drug and clinically or medically significant, recommend that no further doses should be administered at this dose and no dose escalation should proceed. Recommend that enrollment of the study continue at a lower dose or a lower dose cohort may be added to the study. Otherwise, based on the majority vote of the DLRM members, one of the following recommendations may be made: • resume enrollment of the cohort as planned • expand the cohort at the same dose • continue enrollment of the study at a lower dose or add a lower dose cohort to the study

DLRM = Dose Level Review Meeting; CTCAE = common terminology criteria for adverse events.
[a] Subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject or may impact the safety of subjects currently enrolled or of subjects in subsequent cohorts. A decision to stop dosing will not occur without unblinding of the subject's treatment assignment.

7.4.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

7.4.2.1 Amgen Investigational Product: AMG 592

No dosage adjustments are allowed in the study.

7.4.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Appendix 7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

7.6 Treatment Compliance

Subjects will receive the SC doses of study drug (AMG 592 or placebo) at the research facility administered by qualified study personnel for the duration of the study.

7.7 Treatment of Overdose

The effects of overdose of AMG 592 are not known.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken/used from 6 months prior to enrollment through the first dose of investigational product will be collected. For SLE related therapies collect full history of prior treatment. For prior therapies collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant medications are to be collected from first dose of investigational product through the end of safety follow-up period. Collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

7.8.2.1 SLE Therapies

Subjects who were receiving treatment with systemic SLE therapies must maintain a stable dose and the same route of administration through the end of study. No new systemic SLE therapies may be initiated during the study.

7.8.2.2 Corticosteroids

For subjects entering the study while taking oral steroids, no dose adjustments are allowed for 12 weeks. After week 12 new corticosteroids administered by any route may be added or dose adjusted per investigator judgement.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1, Table 2-2) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, disease-related events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Appendix 3.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Disease flare requiring treatment not allowed in the protocol (eg, colitis, asthma)

8.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Appendix 6 for further details). Refer to the Schedule of Activities (Table 2-1 and Table 2-2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable to this study.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1 and Table 2-2).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the **IRT** and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 2 times.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. Subjects rescreening within the original 28-day screening period only need to repeat the assessment(s) that did not originally meet the eligibility criteria; all other initial screening assessments do not need to be repeated. Subjects rescreening after the original 28-day screening period has ended must repeat all screening procedures including being re-consented. However, a tuberculosis test that was negative at the original screening does not need to be repeated as long as the subject has not had exposure to active tuberculosis after the original screening tuberculosis test was completed.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within a visit window of ± 1 day from the scheduled dose date. The date of the first dose of investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Investigational product should be administered after all other study procedures have been completed, except at day 1 and week 12 of the study per the Schedule of Activities (Table 2-1).

If a subject discontinues investigational product early then he/she should complete an early termination visit as outlined in the Schedule of Activities (Table 2-1 and Table 2-2).

9.1.3 Follow-up/Safety Follow-up/End of Study

After the 12 week treatment period, subjects will be followed for an additional 6 weeks up until week 18 for collection of additional safety, PK and PD data as described in the Schedule of Activities (Table 2-2). In the event that a subject terminates the study early (ie, prior to week 18), a safety follow-up visit (6 weeks ± 3 days after the last dose of investigational product) will be performed for collection of adverse events, serious

adverse events, disease-related events, ECG, hematology, and concomitant medications only.

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects must sign and personally date the IRB/IEC and Amgen approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarkers variability and PK of the protocol-required therapies.

9.2.1.3 Medical History

The Investigator or designee will collect a relevant medical and surgical history that started within 5 years or as necessary for chronic or co-morbid conditions prior to enrollment through the start of the adverse event reporting period. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, SLE history must date back to the original diagnosis. The current toxicity grade will be collected for each condition that has not resolved.

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

9.2.1.5 Physical Measurements

Weight in kilograms and height in centimeters should be measured without shoes.

9.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of alcohol and of nicotine or tobacco containing products.

9.2.2 Efficacy Assessments

9.2.2.1 Systemic Lupus Erythematosus Disease Activity Index-2000

The systemic lupus erythematosus disease activity index-2000 (SLEDAI-2K) is a global index that evaluates disease activity and includes 24 items collecting specific manifestations in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular, and hematological. The maximum score is 105.

A SLEDAI score will be used for eligibility purposes but the anti-dsDNA antibodies and serum complement will not count towards the total score. After screening, anti-dsDNA antibodies and serum complement will be counted toward the total SLEDAI-2K score.

Systemic lupus erythematosus disease activity index-2000 descriptors will be scored based on a review of medical history, physical examination, and clinical laboratory findings. Findings should reflect activity during the 10 days prior to the current visit.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Disease-related Events

Disease-related events are defined in Appendix 4.

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational product(s)/study treatment/protocol-required therapies through the safety follow-up visit are recorded using the Event CRF.

All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as serious adverse events and recorded and reported per Sections 9.2.3.1.1.3 and Appendix 4.

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

9.2.3.1.1.2 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE and is described in Appendix 4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the safety follow-up visit are reported using the Event CRF.

9.2.3.1.1.3 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 informed consent through safety follow-up visit are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.4 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 or after end of study. 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 end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

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

The method of recording, evaluating, and assessing causality of adverse events, disease-related events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 4.

9.2.3.1.2 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.

9.2.3.1.3 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 until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

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 Event CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team (SAT) as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, female partners of male subjects will be collected after the start of study treatment and until 6 weeks after the last dose of investigational product.

If a pregnancy 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, and ectopic pregnancy) are considered serious adverse events.

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

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.3.3 Electrocardiograms

At day -1 (baseline) ECGs should be performed**,** prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

Single ECGs will be collected at screening and after day -1 (baseline) as outlined in the Schedule of Activities (Table 2-1). Subject must be in supine position in a rested and

calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG should be performed prior to blood draws or other invasive procedures and must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals.

The PI or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Standard ECG machines should be used for all study-related ECG requirements. Amgen will provide standard ECG machines for use by the site.

9.2.3.4 Home Healthcare Services

The investigator may utilize a qualified home healthcare service provider to conduct the procedures required during study visits, subject to the investigator's direction and sponsor's approval.

The study may include up to 11 home visits, including Week 1, Days 1 (6 hours postdose and 12 hours postdose), 2, 3, 4, and 11, and Week 12, Days 85 (6 hours postdose and 12 hours postdose), 86, 87 and 88. In addition to the assessments listed below, adverse events, serious adverse events, and disease-related events will be collected as per the Schedule of Activities (Table 2-1).

Home visits on Day 1 will include:

- biologic sample collection (PK sampling)
- collection of vital signs
- assessment of changes in signs, symptoms, and concomitant medications

Home visits on Days 2, 3, 4, and 11 will include:

- biologic sample collection (PK and biomarker sampling)
- assessment of substance use
- collection of vital signs
- assessment of changes in signs, symptoms, and concomitant medications

In addition, on Days 2, 4, and 11, PD samples will also be drawn; on Day 2 hematology sample will also be drawn.

Home visits on Day 85 will include:

- biologic sample collection (PK sampling)
- collection of vital signs
- assessment of changes in signs and symptoms

Home visits on Days 86, 87, and 88 will include:

- biologic sample collection (PK sampling)
- assessment of substance use
- collection of vital signs
- assessment of changes in signs, symptoms, and concomitant medications

In addition, on Day 86 a single ECG will be collected.

9.2.4 Clinical Laboratory Assessments

All screening and on-study laboratory samples will be processed and sent to the central laboratory with the exception of urine pregnancy, PPD, and Quantiferon (may be done by central or local laboratory). The central laboratory will be responsible for all screening and on-study serum chemistry, hematology, serum pregnancy, urinalysis, hepatitis C antibody, hepatitis B surface antigen and core antibody, and any other laboratory tests required. Urine pregnancy and PPD testing, if applicable, will be performed locally with kits provided by the central laboratory (except PPD). If Quantiferon testing is performed locally, the central laboratory will also provide kits. The results of this testing will be maintained in the source documents at the site.

Subjects will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests.

Amgen or designee will be responsible for biomarker and pharmacogenetic assessments, and the central laboratory will ship the samples to Amgen or a specialty laboratory for assay (depending on the assessment). The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all samples. All blood samples will be obtained by venipuncture before investigational product administration. The date and time of sample collection will be recorded in the source documents at the site.

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. 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.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

After baseline, PK/PD parameters that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

9.2.4.1 Pregnancy Testing

A highly sensitive serum pregnancy test will be completed at screening and a urine pregnancy test will be completed at baseline prior to 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 Worksheet, see Figure 12-2). Refer to Appendix 5 for contraceptive requirements.

Additional pregnancy testing should be performed at monthly intervals during treatment with investigational product and 6 weeks (± 3 days) after the last dose of investigational product.

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

9.2.4.2 Human Immunodeficiency Virus, Hepatitis B Surface Antigen, and Hepatitis C Antibody

HIV testing at screening will be performed if HIV status is unknown. Subjects will be assessed for hepatitis B surface antigen and hepatitis C virus antibody titers at screening (see Section 6.2). The results of these tests must be negative for inclusion in

the study and will be documented in the source document but will not be recorded on the electronic CRF (eCRF).

9.2.4.3 Prespecified Biomarker Assessments

9.2.4.3.1 C3 and C4 Complement and Anti-dsDNA

Serological tests may be useful in assessing disease activity in SLE. Recent studies have shown an increase in C3, C4 complement (Humrich et al, 2015, He et al, 2016) and a reduction in anti- dsDNA antibodies (He et al, 2016) in SLE patients treated with low dose IL-2. Thus, in the current study, blood samples for the measurement of C3 and C4 complement and anti-dsDNA will be collected as outlined in the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.5 Pharmacokinetic Assessments

All subjects randomized to AMG 592 will have pharmacokinetic samples assessed.

Blood samples will be collected for measurement of serum concentrations of AMG 592 as specified in the Schedule of Activities (Table 2-1, and Table 2-2). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.2.6 Pharmacodynamic Assessments

Lymphocyte subsets: Blood samples will be collected for all subjects at the time points indicated in the Schedule of Activities (Table 2-1 and Table 2-2). These samples will be used to evaluate Treg, Tcon, and NK cells.

Detailed instructions on sample collection, processing, and shipping will be provided in a separate manual.

9.2.7 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of inflammatory conditions and/or to identify subjects who may have positive or negative response to AMG 592. Additional samples are not collected for this part of the study. For subjects who consent to these analyses, DNA may be extracted.

The final disposition of samples will be described in Appendix 6.

9.2.8 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Table 2-1 and Table 2-2) for the measurement of anti-AMG 592 binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized. Additional blood samples may be obtained to rule out anti-AMG 592 antibodies during the study.

Subjects who test positive for anti-AMG 592 antibodies that cross-react with and neutralize native human IL-2 at the final scheduled study visit will be asked to return for additional follow up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result until: (1) Interleukin-2 neutralizing antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of AMG 592. All follow-up results, both positive and negative will be communicated to the sites. This notification is independent of and may be in advance of the time point when the entire study is planned to be unblinded. Refer to Section 7.3 for additional information regarding unblinding. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive AMG 592.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-AMG 592 antibody response may also be asked to return for additional follow-up testing. Refer to the Schedule of Activities (Table 2-1 and Table 2-2), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions.

9.2.9 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 592.

Blood samples are to be collected for biomarker development at the time points specified in the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.10 Other Assessments

9.2.10.1 Tuberculosis Testing

All subjects must receive either a PPD or Quantiferon test at screening per Section 6.2.

9.2.10.1.1 PPD

If a subject does not receive a Quantiferon test, then a PPD test must be performed per Section 6.2. The PPD test must be read by a trained healthcare professional 48 to 72 hours after the test is placed. Purified protein derivative reader must be identified on the delegation of authority for this responsibility.

9.2.10.1.2 Quantiferon

If a subject does not receive a PPD test, then a Quantiferon test must be performed per Section 6.2. Please refer to the central laboratory manual for instructions on sample collection, processing, and shipping of samples (if applicable).

9.2.10.1.3 Chest X-Ray

Subjects with a positive PPD test with a history of Bacillus Calmette-Guerin vaccination or subjects with a positive PPD test (without a history of Bacillus Calmette-Guerin vaccination) or a positive or indeterminate Quantiferon test will require a chest radiograph including posterior-anterior and lateral views. The radiograph report should be read by a radiologist or per local requirement and the report must be reviewed by the investigator before enrollment of the subject.

9.2.10.2 Peripheral Blood Mononuclear Cell

Blood samples will be collected for subjects in the study at the time points indicated in the Schedule of Activities (Table 2-1 and Table 2-2) for peripheral blood mononuclear cell (PBMC) collection. Detailed instructions on sample collection, processing, and shipping will be provided in a separate manual.

10. Statistical Considerations

10.1 Sample Size Determination

Within each cohort subjects will be randomized to AMG 592 or placebo in a 5:2 ratio for cohorts 1, 2 and 3 and in a 3:1 ratio for cohorts 4 and 5. It is planned that approximately 29 subjects will be enrolled with 7 subjects assigned to each cohort (5 to AMG 592 and 2 to placebo) for cohorts 1, 2 and 3 and 4 subjects assigned to cohorts 4 and 5 (3 to AMG 592 and 1 to placebo). The total sample size may exceed 29 subjects and the

number of subjects within a cohort may exceed the planned cohort size if, following a DLRM recommendation, additional dosing cohorts are added and/or existing cohorts are expanded, or if subjects are replaced as per Section 5.2.1. If additional subjects are added to a cohort the randomization ratio may not be preserved.

The sample size is based on practical considerations. With 5 subjects receiving AMG 592 per cohorts 1, 2, and 3, there is a 76% chance of at least 1 subject experiencing an adverse event, if the true event rate is 25%. The chance of at least 1 subject experiencing an adverse event will be 67% if the event rate becomes 20%. With a total of 21 subjects planned to receive AMG 592 in **the study**, there is a 19% chance of at least 1 subject experiencing an adverse event with a true event rate of 1%. The chance of at least 1 subject experiencing an adverse event will be 66% if the true event rate becomes 5%.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

10.2.1.1 Safety Analysis Set

The safety analysis set will consist of all subjects who received at least 1 dose of investigational product. Safety analysis set will be used for analyses unless otherwise specified. Subjects will be analyzed according to the actual treatment received.

10.2.1.2 Pharmacokinetic Concentration Analysis Set

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

10.2.1.3 Pharmacokinetic Parameter Analysis Set

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

10.2.1.4 Pharmacodynamic Analysis Set

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

10.2.2 Covariates

There are no pre-specified covariates.

10.2.3 Subgroups

There are no pre-specified subgroup analyses.

10.2.4 Handling of Missing and Incomplete Data

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

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.3.1 Planned Analyses

There are no interim analyses planned for **this study**. The **final** analysis will be done after all subjects have completed the study (ie, safety follow-up).

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

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

10.3.2.2 Efficacy Analyses

As an exploratory endpoint, SLEDAI-2K score and change from baseline will be provided at all time points collected.

10.3.2.3 Safety Analyses

10.3.2.3.1 Analyses of Primary Endpoint(s)

The primary endpoint for this study is safety. Safety analysis set will be used for analyses included in this section. Please refer to Section 10.3.2.3.2 to 10.3.2.3.8 for analyses of safety endpoints.

10.3.2.3.2 Adverse Events and Disease-related Events

Subject incidence of all treatment-emergent adverse events will be tabulated by 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 incidence of disease-related events, fatal disease-related events, and device-related events, if applicable, will be tabulated by system organ class and preferred term.

10.3.2.3.3 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics at selected time points by treatment group. Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated.

10.3.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics at selected time points by population and treatment group. Shifts in vital sign values between the baseline and the worst on-study value will be tabulated.

10.3.2.3.5 Physical Measurements

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

10.3.2.3.6 Electrocardiogram

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

10.3.2.3.7 Exposure to Investigational Product

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

10.3.2.3.8 Exposure to Concomitant Medication

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

10.3.2.4 Other Analyses

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

10.3.2.4.1 Pharmacokinetic Analysis

Pharmacokinetic concentration data will be analyzed using PK concentration analysis set. Individual serum concentration-time plots for AMG 592 will be

presented for each subject as well as mean concentration-time plots for each treatment.

Pharmacokinetic parameters will be analyzed using PK parameter analysis set.

10.3.2.4.2 Antibody Formation

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

10.3.2.4.3 Exploratory Endpoints

All exploratory endpoints will be summarized using descriptive statistics. The change from baseline and/or fold change from baseline may also be summarized.

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12. Appendices

Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ACR	American College of Rheumatology
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Anti-dsDNA	Anti-double stranded DNA
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{tau}	area under the concentration-time curve over a dosing interval
BIL	bilirubin
BLRM	Bayesian logistic regression model
CBC	complete blood count
cGvHD	chronic graft versus host disease
CIOMS	Council for International Organizations of Medical Sciences
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CRF	case report form
CTCAE	common terminology criteria for adverse events
DILI	drug-induced liver injury
DLRM	dose level review meeting
ECG	Electrocardiogram
EDC	electronic data capture
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, safety follow-up), as applicable
eCRF	electronic CRF
FIH	first in human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GVHD	graft versus host disease
HepCAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation or Term	Definition/Explanation
HIV	Human Immunodeficiency Virus
HRT	hormonal replacement therapy
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG	immunoglobin G
IL-2	Interleukin-2
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IQR	interquartile range
IRB	Institutional Review Boards
IRT	interactive response technology that is linked to a central computer in real time as an interface to collect and process information
MAD	multiple ascending dose
MDRD	Modification of Diet in Renal Disease
NK cells	natural killer cells
NKT cells	natural killer T cells
NOAEL	no observed adverse effect level
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	Pharmacokinetic
PPD	purified protein derivative
PR Interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
QRS interval	QRS interval is the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate using accepted methodology
QW	every week
Q2W	every other week
RA	rheumatoid arthritis
RBC	red blood cell
SAT	safety assessment team

Abbreviation or Term	Definition/Explanation
SC	subcutaneous
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
SRI-4	Systemic Lupus Erythematosus Responder Index-4
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
Tcon	conventional T cell
Teff	T effector cells
T_{max}	time of maximum observed concentration
Treg	regulatory T cells
ULN	upper limit of normal
US	United States

Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central laboratory and/or by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 6.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Central Laboratory			
Chemistry	Urinalysis	Hematology	Other Labs
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine[a] Total bilirubin Direct bilirubin ALP AST (SGOT) ALT (SGPT)	Specific gravity pH Blood Protein (reflex urine protein to creatinine ratio if +1) Glucose Ketones Urobilinogen Bilirubin Microscopic (reflex testing if abnormal)	Red blood cells Antinuclear antibody Hemoglobin Hematocrit MCV MCH MCHC RDW Reticulocytes Platelets White blood cells WBC Differential • Total neutrophils or segmented neutrophils • Bands • Eosinophils • Basophils • Lymphocytes • Monocytes	Central Laboratory: Quantiferon[b] Hepatitis B surface Antigen Hepatitis B core antibody Hepatitis C virus antibody HIV FSH[c] Serum pregnancy[d] Anti-dsDNA C3 and C4 complement Lymphocyte subsets PBMC AMG 592 PK Anti-AMG 592 antibodies Biomarker development Pharmacogenetics sample SLE drug levels Urine drug/alcohol screen Local Laboratory: Urine Pregnancy PPD

ALT = alanine aminotransferase; Anti-dsDNA = anti-double stranded deoxyribonucleic acid; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HIV = human immunodeficiency virus; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RDW = red cell distribution width; PBMC = peripheral blood mononuclear cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count; MDRD = Modification of Diet in Renal Disease; PK = pharmacokinetics; FSH = Follicle stimulating hormone; PPD = purified protein derivative

[a] Glomerular filtration rate will be calculated by MDRD formula

[b] Quantiferon testing can be done locally or by the central laboratory

[c] Can be done as a part of the clinical chemistry

[d] Only at screening

After baseline, pharmacokinetics (PK)/pharmacodynamics (PD) parameters that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Appendix 3. Study Governance Considerations

Dose Level Review Meetings and Data Review Team

Dose Level Review Meetings

The study will employ Dose Level Review Meetings (DLRM). The DLRM team will be composed of the investigator(s), Amgen Medical Monitor, and Amgen Global Safety Officer or designee. Other optional Amgen representatives (eg, Amgen biostatistics representative, Clinical Trial Manager) may be included as appropriate. A quorum, defined as > 50% of the participating investigators who have enrolled at least 1 subject in the study or their qualified designee (ie, sub-investigator or research nurse or study coordinator possessing hard copy documentation [eg, email] of the investigator's vote regarding the dose level review), must be in attendance for the DLRM. The DLRM will be rescheduled if a quorum is not reached.

Voting members of the DLRM will include the Amgen medical monitor, the Amgen global safety officer or designated safety scientist, and all participating investigators or their qualified medical doctor designee(s). The majority opinion of the investigators will count as 1 vote; the medical monitor will cast 1 vote and the global safety officer will cast 1 vote. A majority positive vote indicating an acceptable safety profile for the investigational product is required to allow dose level escalation or modification and/or cohort continuation/expansion to proceed. All available study data including demographics, medical history, concomitant medications, adverse events, electrocardiograms, vital signs, laboratory results, and emerging pharmacokinetic and pharmacodynamics data will be reviewed. Data to be reviewed may be unqueried. Study investigators will be informed of DLRM dosing decisions via email notification. Only in the following limited circumstances, dose decisions can be made by the Amgen Medical Monitor and Amgen Global Safety Officer without convening a DLRM:

- The Amgen Medical Monitor and Amgen Global Safety Officer may decide to begin the next cohort using a de-escalated dose (de-escalated from the dose level of the most recent cohort), if this de-escalated dose had been previously evaluated during a DLRM.

Regulatory and Ethical Considerations

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

- 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 Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board/International Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, 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 will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the [IRB/IEC] 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 informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

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 informed consent form is to be signed and personally dated by the subject 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; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject.

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 28 days from the previous informed consent form signature date.

The informed consent form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

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 case report form (CRF) 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 informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC 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.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All persons designated as authors must qualify for authorship, and all those who qualify are to be listed.

Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF 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 per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case report forms must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT (if used, such as subject identification and randomization number) and CRF entries if the

CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including [Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable]
- Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee 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 GCP.

Both Amgen 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 IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Disease-related Event

Disease-related Event Definition
Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. See Section 9.2.3.1.1.1 for the list of disease-related events. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. Disease-related events that would qualify as an adverse event or serious adverse event: ○ An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event. Disease-related events that do not qualify as adverse events or serious adverse events: ○ An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

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.
Events Meeting the Adverse Event Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], 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. "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

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.
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, Disease-related Events (if applicable), and Serious Adverse Events

Adverse Event, Disease-related Event, and Serious Adverse Event Recording

When an adverse event, disease-related 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/disease-related event/serious adverse event information in the Event case report form (CRF).

- Additionally, the investigator is required to report a fatal disease-related event on the Event CRF.

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 investigational product, other protocol-required therapies; 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 Event CRF.

It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event CRF 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 Amgen.

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 be based on:

The Common Terminology Criteria for Adverse Events (CTCAE), version 4.0**3** which is

available at the following location:

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

Assessment of Causality

The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, 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 Amgen 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 Amgen.

If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed Event CRF.

The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an Electronic Serious Adverse Event Contingency Form (paper form; see Figure 12-1) within 24 hours of the investigator's knowledge of the event. The site will enter the serious adverse event data into the electronic system as soon as it becomes available. After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on an Electronic Serious Adverse Event Contingency Form (paper form; see Figure 12-1).

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

AMGEN Study # 20170103 AMG 592	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

US: [illegible]

1. SITE INFORMATION

Site Number	Investigator	Country

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		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term:
and start date: Day ____ Month ____ Year ______

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day Month Year

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report 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	Is event serious?	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? AMG 592 No/ Yes/	[redacted]	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg. biopsy
				☐Yes ☐No					
				☐Yes ☐No					
				☐Yes ☐No					

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

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose 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 # ____ ☐ Unavailable / Unknown

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Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

AMGEN Study # 20170103 AMG 592	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any 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											

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

Date (Day Month Year)	Additional Tests	Results	Units

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

AMGEN Study # 20170103 AMG 592	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. 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 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for female of childbearing potential are outlined in Section 6.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 6 weeks (± 3 days) after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 6 weeks (± 3 days) after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet 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 Worksheet 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 6 weeks (± 3 days) after the last dose of the study drug. 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 event 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 Amgen 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 4. 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 investigational product (see Section 8.1 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 6 weeks (± 3 days) after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) 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 Worksheet 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

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 6 weeks after the last dose of investigational product.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 226.
- With the female subjects 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 6 weeks after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

Amgen Proprietary - Confidential

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: 20170103

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 12-2. Pregnancy and Lactation Notification Worksheet

Amgen Proprietary - Confidential

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: 20170103

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:** _____

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Appendix 6. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Activities (Table 2-1 and Table 2-2) 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.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the inflammatory conditions, the dose response and/or prediction of response to AMG 592, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Appendix 3 for subject confidentiality.

Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

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 (BIL) 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)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3 x ULN at any time	> 2 x ULN
		OR
INR	--	> 1.5 x ULN (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8 x ULN at any time	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values
	> 5 x ULN but < 8 x ULN for ≥ 2 weeks	
	> 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule	> 3 x ULN (when baseline was < ULN)
	> 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	
	OR	
ALP	> 8 x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then investigational product is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen 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 case report form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

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 4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, BIL (total and direct), and INR within 24 hours
- In cases of TBL > 2 x ULN or INR > 1.5, retesting of liver tests, BIL (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 or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

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, antinuclear 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 non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase (CPK), 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, and INR) until all laboratory abnormalities return to baseline or normal or 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 DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

Superseding Amendment 5

Protocol Title: A Randomized, Double-blind, Placebo-controlled Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Multiple Ascending Subcutaneous Doses of AMG 592 in Subjects With Systemic Lupus Erythematosus

Amgen Protocol Number 20170103

Amendment Date:	23 April 2020
Superseding Amendment Date:	25 June 2020

Rationale:

The current protocol (amendment 4) is designed as a seamless phase 1b/2a study to evaluate the safety and efficacy of AMG 592 in subjects with active systemic lupus erythematosus.

The phase 2a will now be converted into a phase 2b. Due to the complexity of the new phase 2b design, it was decided that splitting the study into 2 protocols would avoid logistical problems for clinical development and clinical operations (vendors, etc). Having separate protocols also alleviates any possibility of unblinding in a shared database.

The following changes were made to the superseding protocol dated 25 June 2020:

It was noted that in the amendment process for protocol amendment 1, the exploratory endpoints for the phase 1b portion of the study were accidentally deleted. These have been added back to support the analyses of these endpoints.

Amendment 5

Protocol Title: A Randomized, Double-blind, Placebo-controlled Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Multiple Ascending Subcutaneous Doses of AMG 592 in Subjects With Systemic Lupus Erythematosus

Amgen Protocol Number 20170103

Amendment Date: 23 April 2020

Rationale:

The current protocol (amendment 4) is designed as a seamless phase 1b/2a study to evaluate the safety and efficacy of AMG 592 in subjects with active systemic lupus erythematosus (SLE) with inadequate response to standard of care therapy.

The study has become part of the Food and Drug Administration (FDA) Complex Innovative Design (CID) pilot program. With the opportunity to implement a CID to the SLE development program, the phase 2a is now a phase 2b. Due to the complexity of the new phase 2b design, it was decided that split the study into 2 protocols would avoid logistical problems for clinical development and clinical operations (vendors, etc). Having separate protocols also alleviates any possibility of unblinding in a shared database.

In addition, it was noted that in the amendment process for protocol amendment 1, the exploratory endpoints for the phase 1b portion of the study were accidentally deleted. These have been added back to the protocol, with some additional text to support the analyses of these endpoints.

Superseding Amendment 4

Protocol Title: A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Systemic Lupus Erythematosus With Inadequate Response to Standard of Care Therapy

Amgen Protocol Number (AMG 592) 20170103

NCT Number: NCT03451422

EudraCT Number 2017-002564-40

Amendment Date: 24 February 2020

Rationale:

This superseding amendment is to address administrative details that were erroneously included in protocol amendment 4 dated 06 February 2020.

Amendment 4

Protocol Title: A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Systemic Lupus Erythematosus With Inadequate Response to Standard of Care Therapy

Amgen Protocol Number (AMG 592) 20170103

NCT Number: NCT03451422

EudraCT Number 2017-002564-40

Amendment Date: 06 February 2020

Rationale:

This protocol is being amended to add 2 additional dosing cohorts to the phase 1b part of the protocol in order to investigate whether treatment with higher doses of AMG 592 is safe and may result in greater Treg expansion with continued maintenance of selectivity. This amendment also allows re-enrollment of previously enrolled study subjects provided they meet additional entry criteria.

Amendment 3

Protocol Title: A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Systemic Lupus Erythematosus With Inadequate Response to Standard of Care Therapy

Amgen Protocol Number (AMG 592) 20170103

NCT Number: NCT03451422

EudraCT Number: 2017-002564-40

Amendment Date: 18 November 2019

Rationale:

This protocol is being amended to add language for home healthcare provided services and to remove Amgen retired template language in regards to self-evident corrections.

Amendment 2

Protocol Title: A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Systemic Lupus Erythematosus With Inadequate Response to Standard of Care Therapy

Amgen Protocol Number: AMG 592 20170103

Amendment Date: 12 June 2019

Rationale:

The rationale for this protocol amendment is:

1. To update the phase 1b sample size language throughout the protocol to allow flexibility for expansion and/or addition of cohorts per DLRM recommendation, for replacement of subjects who discontinue investigational drug product prior to completing week 4 of the study and to allow enrollment of additional eligible screened subjects in each cohort.
2. To allow subjects to meet entry criteria with a history of positive ANA and anti-dsDNA antibody rather than positive results at screening because these tests may wax and wane in SLE patients.
3. To update the Risk Assessments section of the protocol to align with recent change to the Investigator's Brochure.
4. To update the dose for cohort 3, from [redacted] µg [redacted] to [redacted] µg [redacted] in order to allow exploration of a wider dose range in the phase 1b part of the study. Administration of the [redacted] µg [redacted] dose to all subjects in cohort 2 has been completed through the DLRM evaluation period. Blinded review has revealed no concerning safety signals and investigational product (AMG 592 or placebo) has been generally well-tolerated. These data provide justification for consideration of dose escalation to the [redacted] µg [redacted] dose.

Amendment 1

Protocol Title: A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Systemic Lupus Erythematosus With Inadequate Response to Standard of Care Therapy

Amgen Protocol Number (AMG 592) 20170103

NCT Number: NCT03451422

EudraCT Number 2017-002564-40

Amendment Date: 26 July 2018

Rationale:

This protocol is being amended to change subject urine drug/alcohol testing, during screening, from the local laboratory to the central laboratory.