Title Page

Protocol Title:		A Phase 2b Dose Ranging Study to Evaluate the Efficacy and Safety of Rozibafusp Alfa **(**AMG 570**)** in Subjects With Active Systemic Lupus Erythematosus (SLE) With Inadequate Response to Standard of Care (SOC) Therapy
Short Protocol Title:		Safety and Efficacy of AMG 570 in Subjects With Active Systemic Lupus Erythematosus (SLE)
Protocol Number:		20170588
Investigational Product:		Rozibafusp Alfa (AMG 570)
Sponsor	**Name of Sponsor:**	Amgen Inc.
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EudraCT Number:		2019-000328-16
NCT Number:		04058028
Protocol Date:		**Document Version** / **Date** Original / 26 February 2019 Amendment 1 / 28 February 2020 Amendment 2 / 13 October 2020 Superseding Amendment 2 / 11 November 2020 **Amendment 3** / **24 May 2022**
Version/Date:		**Data Element Standards Version** 6.1

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 2b Dose Ranging Study to Evaluate the Efficacy and Safety of Rozibafusp Alfa (AMG 570) in Subjects With Active Systemic Lupus Erythematosus (SLE) With Inadequate Response to Standard of Care (SOC) Therapy, dated **24 May 2022**, and agree to abide by all provisions set forth therein.

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

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my sub investigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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 Phase 2b Dose Ranging Study to Evaluate the Efficacy and Safety of Rozibafusp Alfa (AMG 570) in Subjects With Active Systemic Lupus Erythematosus (SLE) With Inadequate Response to Standard of Care (SOC) Therapy
Short Protocol Title: Safety and Efficacy of AMG 570 in Subjects With Active Systemic Lupus Erythematosus (SLE)

Study Phase: 2b

Indication: systemic lupus erythematosus (SLE)

Rationale:

This is a phase 2b dose-ranging study to assess efficacy and safety of rozibafusp alfa (AMG 570) in subjects with active SLE. AMG 570 could be a viable treatment option for SLE patients who are not responding to current standard of care.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• Evaluate the efficacy of AMG 570 at week 52 as measured by the Systemic Lupus Erythematosus **(SLE)** Responder Index (SRI-4)	• SRI-4 response at week 52
The primary estimand is the difference in SRI-4 response between each AMG 570 dose group and placebo at week 52 for all subjects with SLE with inadequate response to SOC therapy who are randomized, regardless of **investigational product** discontinuation; subjects using more than protocol-allowed therapies will be considered as non-responders.	
Secondary	
• Evaluate the efficacy of AMG 570 at week 24	• SRI-4 response at week 24 • **British Isles Lupus Assessment Group (**BILAG**)** based Combined Lupus Assessment (BICLA) response at week 24
• Evaluate the efficacy of AMG 570 at week 52	• Lupus Low Disease Activity State (LLDAS) response at week 52 • BICLA response at week 52
• Evaluate the efficacy of AMG 570 as measured by SRI-4 response with oral corticosteroid (OCS)-tapering	• SRI-4 response at week 52 with reduction of OCS to $\leq$ 7.5 mg/day by week 44 and sustained through week 52 in subjects with a baseline OCS dose $\geq$ 10 mg/day

Objectives	Endpoints
• Evaluate the efficacy of AMG 570 on disease flares	• Annualized moderate and severe flare rate (as measured by SELENA-SLEDAI Flare Index) over 52 weeks • Annualized severe flare rate (as measured by SELENA-SLEDAI Flare Index) over 52 weeks • Annualized flare rate (as measured by BILAG score designation of "worse" or "new" resulting in a B score in ≥ 2 organs or an A score in ≥ 1 organ) over 52 weeks
• Evaluate the efficacy of AMG 570 on joints and skin	• Total tender and swollen joint count (limited to hands and wrists): ≥ 50% improvement from baseline at week 12, 24, 36, and 52 in subjects with ≥ 6 tender and swollen joints **in** hands and wrists at baseline • Cutaneous Lupus Erythematosus Area and Severity Index (CLASI) activity score**:** ≥ 50% improvement from baseline at week 12, 24, 36, and 52 in subjects with a CLASI activity score ≥ 8 at baseline
• Describe the efficacy of AMG 570 using patient reported outcomes	• Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a Instrument (PROMIS-Fatigue SF7A) score and change from baseline at week 12, 24, 36, 44, and 52 • Medical Outcomes Short Form 36 version 2 Questionnaire (SF-36v2) change from baseline **in the physical component** score**, mental component score individual domains of the Medical Outcomes Short Form 36 version 2 questionnaire (SF-36v2)** at week 12, 24, 36, 44, and 52 • Lupus **Quality of Life questionnaire (Lupus**QoL**)** score and change from baseline at week 12, 24, 36, 44, and 52 • Patient Global Assessment (PtGA) score and change from baseline at week 12, 24, 36, 44, and 52

Objectives	Endpoints
• Characterize the safety of AMG 570	• Treatment-emergent adverse events • Serious adverse events • Clinically significant changes in laboratory values and vital signs
• To characterize the pharmacokinetics (PK) of AMG 570	• Trough serum concentrations and terminal elimination half-life of AMG 570
Exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

Hypothesis

AMG 570 administered for 52 weeks will be well tolerated and have greater efficacy than placebo as measured by **Systemic Lupus Erythematosus Responder Index (**SRI-4**)**

response at week 52 in subjects with active SLE and an inadequate response to standard of care therapy.

Overall Design

This is a Bayesian adaptive phase 2b, multi-center, double-blind, randomized, placebo-controlled, 52-week, dose-ranging study in subjects with active SLE and inadequate response to SOC therapies including **oral corticosteroids (**OCS**)**, immunosuppressants, and immunomodulators. Subjects will be randomized to receive either placebo or 1 of 3 doses of AMG 570 with the last dose at week 50. **Treatment will be administered every 2 weeks (Q2W).** Study duration for a single subject will be 52 weeks plus the screening period and safety follow-up period. Tapering of OCS from the baseline dose **is** allowed **up to** week 44 **at the discretion of the investigator**. The first interim analysis (IA) will be executed after the first 40 enrolled subjects have had the opportunity to complete the week 24 assessment. Additional IAs may be executed after approximately every 32 newly enrolled subjects have had the opportunity to complete the week 24 assessment. The last IA will occur when all 320 subjects are randomized and have had the opportunity to complete the week 24 assessment. This IA will be referred to as the 'all-subjects-week-24 IA'. The purpose and analyses planned at each IA are listed in Table 1-1.

Number of Subjects

Approximately 320 subjects will be enrolled. Because enrollment can be stopped if early stopping rules for futility are met, the actual sample size could be smaller.

Summary of Subject Eligibility Criteria

Eligible subjects must be between the ages of 18 and 75 years of age, inclusive, and be able to provide informed consent. Subjects must fulfill the classification criteria for SLE according to the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for SLE, with antinuclear antibody ≥ 1:80 by immunofluorescence on Hep-2 cells being present at screening. In addition, at screening, subjects must have a **Hybrid Systemic Lupus Erythematosus Disease Activity Index (**hSLEDAI**)** ≥ 6 and a clinical hSLEDAI ≥ 4. Subjects must be on a stable dose of OCS (≤ 20mg/day of prednisone or equivalent) for ≥ 2 weeks prior to screening and stable dose of other standard treatment for SLE such as immunosuppressants/immunomodulators for ≥ 8 weeks prior to screening. Subjects with active or unstable neuropsychiatric SLE or unstable lupus nephritis, or any disease other

than SLE requiring treatment with oral or parenteral corticosteroids for more than 2 weeks within 6 weeks of the screening visit or any clinically significant concurrent medical conditions and/or significant laboratory abnormalities will not be eligible (Section 6.2). Female subjects must not be pregnant or breastfeeding or plan to become pregnant or breastfeed during treatment or for at least 10 additional weeks after the last dose of investigational product in the study.

For a full list of eligibility criteria, please refer to Sections 6.1 to 6.3.

Treatments

AMG 570 and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical investigational product distribution procedures. Both are liquid formulations presented in identical glass vials and stored in the same manner. AMG 570 or placebo will be administered by subcutaneous (SC) injection Q2W by the Principal Investigator (PI) or appropriately trained designee.

Procedures

Written informed consent must be obtained from all subjects (or his/her legally authorized representative) before any study-specific screening procedures are performed. The following procedures will occur per the Schedule of Activities: medical history; physical examination; physical measures; vital signs; prior and concomitant medication assessment; tuberculosis testing; urinalysis; and blood draw for serum chemistry, hematology, Human Immunodeficiency Virus (HIV) antibodies, hepatitis B and C testing, [redacted], biomarker development, and pharmacogenetics sampling. Women of childbearing potential will have pregnancy tests performed at screening and at regular intervals during the study. Disease assessments (hSLEDAI, BILAG, **Physician Global Assessment [**PGA**]**, swollen and tender joints count, **Cutaneous Lupus Erythematosus Area and Severity Index [**CLASI**]**, photography of skin lesions in selected cases, and patient reported outcomes) will also be obtained. Safety assessments including adverse events, serious adverse events, and clinically significant changes in laboratory values and vital signs will be performed throughout the entire study including 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 2-2.

Statistical Considerations

A total of approximately 320 subjects will be randomized to receive AMG 570 at 70 mg Q2W, 280 mg Q2W, 420 mg Q2W, or placebo. The approximate sample size of 320 is chosen to provide 80% power to detect ≥ 25% absolute improvement for at least 1 AMG 570 dose group relative to placebo in the primary endpoint of SRI-4 response rate at week 52 at a significance level of 0.025 (1-sided) using a Bayesian Hierarchical Model, assuming a 40% response rate in the placebo group.

Randomization will be stratified by geographic region and screening hSLEDAI score (≥ 10 or < 10) and start with a fixed and equal allocation (1:1:1:1). At the time of the IAs (if before full enrollment), the randomization probability for each of the 3 active doses may be updated based on clinical efficacy, while the randomization allocation probability to placebo will be kept constant, ie, 25%. IAs will be conducted as described in Table 1-1. IAs will be implemented by an Independent Biostatistics Group (IBG) as described in Appendix 3 with decision rules specified in Section 10.3.1.1.

The primary analysis of the primary endpoint, SRI-4 at week 52, will be based on a Bayesian Hierarchical Model which borrows dynamically in order to share information across the 3 active AMG 570 treatment groups while controlling the overall type I error at the 1-sided 2.5% level across multiple comparisons.

Categorical variables will be summarized using the number and percent of subjects falling into each category. All continuous variables will be summarized using mean, standard error or standard deviation, median, minimum, maximum, and number of subjects with observations. Safety endpoints will be summarized descriptively.

Table 1-1. Analyses Schedule: Decisions at each Interim Analysis, Primary Analysis, and Final Analysis

Time point	Adaptive Decision	Number of subjects with opportunity to complete week 24
1st IA	RAR	40
2nd IA	Futility, RAR	72
3rd IA	Futility, RAR	104
4th IA	Futility, RAR	136
5th IA	Futility, RAR	168
6th IA	Futility, RAR	200
7th IA[a]	Futility, RAR	232

Last IA[b]	Administrative Success	320
Primary Analysis	Not applicable	All subjects have had the opportunity to complete week 52
Final Analysis	Not applicable	All subjects reach EOS

IA = interim analysis; RAR = response adaptive randomization; EOS= end of study

[a] **Interim analyses are planned after every 32 subjects are randomized and have had the opportunity to complete the week 24 assessment until full enrollment. Number of IAs will depend on the actual enrollment rate.**

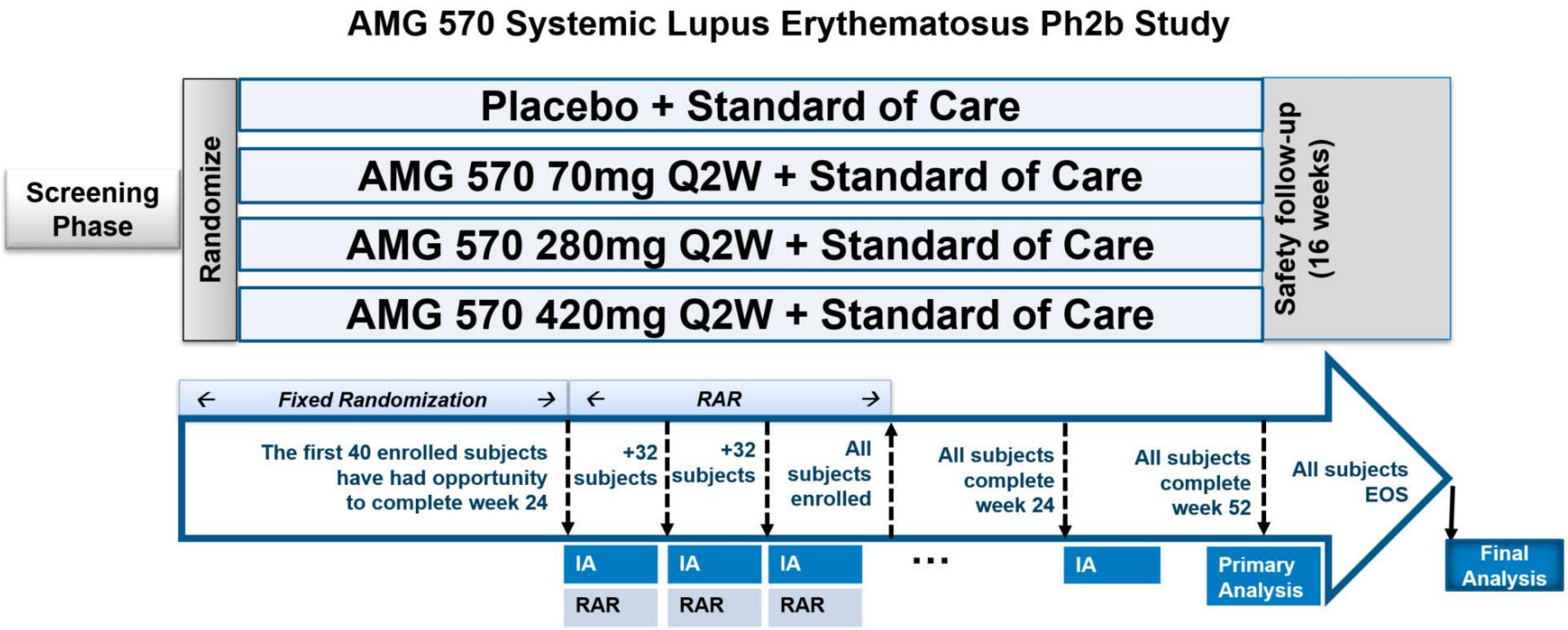
[b] Last IA is the all-subjects-week-24 IA. The administrative success analysis at the last IA will not result in any adaptive decision for the ongoing study.

Refer to Section 10 for a full description of the statistical analysis methods.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



EOS = end of study; IA = interim analysis; Q2W = every 2 weeks; RAR = Response Adaptive Randomization.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities – Treatment Period

	Screening	Treatment Period																													
Study Week		Baseline visit/Day 1			2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52/ET
Study Day ± Visit Window	Scr visit	1 (pre-rand)	1 (pre-dose)	1 (dose)	15 ±3	29 ±3	43 ±3	57 ±3	71 ±3	85 ±3	99 ±3	113 ±3	127 ±3	141 ±3	155 ±3	169 ±3	183 ±3	197 ±3	211 ±3	225 ±3	239 ±3	253 ±3	267 ±3	281 ±3	295 ±3	309 ±3	323 ±3	337 ±3	351 ±3	365 ±3
GENERAL AND SAFETY ASSESSMENTS																															
Informed consent	X																														
Eligibility	X	X																													
Demographics	X																														
Physical exam	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X	
2019 EULAR / ACR criteria	X																														
Height	X																														
Weight	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X	
Medical history[a]	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				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	
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	X	X	X

Footnotes defined on last page of the table.

Table 2-1. Schedule of Activities – Treatment Period

Study Week	Screening	Treatment Period																														
		Baseline visit/Day 1			2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52/ET
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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	X	X	X	X	X	X	X	X
GENERAL AND SAFETY ASSESSMENTS (Continued)																																
Randomization[d]			X																													
Home Health Visit[e]															X		X		X		X		X		X		X		X		X	
LABORATORY ASSESSMENTS																																
Serum pregnancy test	X																															
Urine pregnancy test			X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
Tuberculosis test[f]	X																															
Hepatitis B & C[g]	X																															
HIV serology	X																															
Blood SLE SOC drug levels[h]	X																															
Antinuclear antibody	X																															
[redacted]																																

Footnotes defined on last page of the table.

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Coagulation testing[k]	X		X													X															X
Hematology[i]	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
ESR[l]	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
Chemistry[i]	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
LABORATORY ASSESSMENTS (Continued)																																
Urinalysis[m]	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
Urine protein/ creatinine[m]	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
SLE CLINICAL ASSESSMENTS																																
Tender/swollen joint count[n]	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
PGA VAS[o]	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
hSLEDAI	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
Clinical hSLEDAI	X	X																														
SELENA-SLEDAI Flare Index			X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
BILAG	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		X

Footnotes defined on last page of the table.

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Study Week	Screening	Treatment Period																														
		Baseline visit/Day 1			2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52/ET
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CLASI activity and damage	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		X
SDI			X													X																X
Photography[p]			X							X						X															X
IMMUNOGENICITY																																
[redacted]																																
BIOMARKER AND PHARMACOGENETICS																																
[redacted]																																
Biomarker development sample[i]			X			X				X						X						X				X						X
Pharmaco-genetics [i, s]			X																													
CLINICAL OUTCOME ASSESSMENTS: PATIENT REPORTED OUTCOMES																																
SF-36v2[t]			X			X				X						X						X				X						X
PROMIS-Fatigue[t]			X			X				X						X						X				X						X
LupusQoL[t]			X			X				X						X						X				X						X
Patient Global Assessment (PtGA)[t]			X			X				X						X						X				X						X

Footnotes are defined on last page of the table.

Table 2-1. Schedule of Activities – Treatment Period

Study Week	Screening	Treatment Period																														
		Baseline visit/Day 1			2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52/ET
Study Day ± Visit Window	Scr visit	1 (pre-rand)	1 (pre-dose)	1 (dose)	15 ±3	29 ±3	43 ±3	57 ±3	71 ±3	85 ±3	99 ±3	113 ±3	127 ±3	141 ±3	155 ±3	169 ±3	183 ±3	197 ±3	211 ±3	225 ±3	239 ±3	253 ±3	267 ±3	281 ±3	295 ±3	309 ±3	323 ±3	337 ±3	351 ±3	365 ±3
INVESTIGATIONAL PRODUCT ADMINISTRATION																																
Investigational Product (AMG 570/ placebo)[u]				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			
PHARMACOKINETIC ASSESSMENTS																																
PK samples[i, q]			X			X		X		X		X		X		X						X				X					X	

ACR = American College of Rheumatology; [redacted] aPTT = activated partial thromboplastin time; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease and Severity Index; Clinical hSLEDAI = hybrid SLEDAI assessment score without the inclusion of points attributable to any laboratory parameter, including urine and immunologic parameters; eCRF = electronic Case Report Form; ESR = erythrocyte sedimentation rate; ET = early termination visit; EULAR = European League Against Rheumatism; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HIV = Human Immunodeficiency Virus; [redacted] INR = international normalized ratio; [redacted] PCR = polymerase chain reaction; PD = pharmacodynamics; PGA = Physician Global Assessment; PK = pharmacokinetic; PPD = purified protein derivative; PROMIS = Patient-reported Outcomes Measures Information System; PT = prothrombin time; PTT = partial thromboplastin time; LupusQoL = Lupus Quality of Life questionnaire; [redacted]; SDI = Systemic Lupus International Collaborating Clinic/American College of Rheumatology Damage Index; Scr = screening; SF-36v2 = Medical Outcomes Short Form 36 version 2 questionnaire; SLE = systemic lupus erythematosus; hSLEDAI = Hybrid Systemic Lupus Erythematosus Disease Activity Index; VAS = visual analogue scale.

[a] Including substance abuse history.

[b] Only for subjects with a positive tuberculosis test (ie, positive PPD [purified protein derivative] or positive or indeterminate QuantiFERON®-TB or T-spot test).

[c] **After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 9.2.3.1.1.3 or additional details.**

[d] Randomization may occur at any time after confirmation of all eligibility criteria, but the maximum time between initiation of screening and randomization is 33 days.

[e] In addition to administration of investigational product, safety assessments including vital signs, adverse events, serious adverse events, and concomitant medications review will be collected. Home health care visits will be optional after week **20** for subjects who do not experience any adverse effects from investigational product administration.

[f] Either a centrally **or locally** performed QuantiFERON®-TB or locally performed PPD or T-spot test will be done during screening per Section 6.2 criterion 206.

[g] For subjects with HBsAg negative, HBcAb positive and undetectable viral DNA by PCR; and for subjects with HCVAb positive and undetectable viral RNA by PCR, serum viral DNA (Hepatitis B virus) or RNA (Hepatitis C virus) will be monitored by PCR in peripheral blood at **approximately** every 3 months during treatment period, and up to **a minimum of** 16 weeks after **last administration of** the **investigational product**.
[h] Blood levels will be measured for the following: azathioprine, mycophenolate mofetil and hydroxychloroquine.
[i] Blood samples must be collected prior to administration of investigational product.
[j] Lupus reflex will be done if aPTT is prolonged.
[k] PT/INR and aPTT (in case of drug-induced liver injury [DILI] events, fibrinogen and D-dimers will also be included).
[l] ESR will be performed at a local laboratory.
[m] Clean catch urine specimen required.
[n] Tender and swollen joint counts will be performed as described in Section 9.2.2.5.
[o] Should be completed by a health care provider before assessing the hSLEDAI and BILAG scores. See Section 9.2.2.6.
[p] Whenever possible and only in subjects with a CLASI activity score ≥ 8 at screening per Section 9.2.2.4.
[q] If a subject discontinues investigational product prior to completing week 52 visit, they should be encouraged to maintain the planned scheduled assessment for monthly efficacy and safety visits through week 52 (Table 2-1). [redacted] and PK samples should be collected at the first 4 visits after investigational product discontinuation.
[redacted]
[s] DNA will be extracted only if subject provides additional consent for pharmacogenetics testing.
[t] Patient reported outcomes should be completed as described in Section 9.2.10.
[u] Investigational product (AMG 570 or placebo) will be administered as described in Section 7.1.1. Subjects will be observed for at least 30 minutes at the site or by the home health care provider following investigational product administration.

Table 2-2. Schedule of Activities – Safety Follow-up Period[a]

Safety Follow-up Week ± Visit Window	4 Weeks ± 5 days after last IP dose	4 Weeks ± 5 days after prior safety follow-up visit	4 Weeks ± 5 days after prior safety follow-up visit	4 Weeks ± 5 days after prior safety follow-up visit EOS
GENERAL AND SAFETY ASSESSMENTS				
Vital signs	X	X	X	X
Adverse events	X	X	X	X
Serious adverse events[b]	X	X	X	X
Concomitant medications review	X	X	X	X
LABORATORY ASSESSMENTS				
Urine pregnancy test	X	X		
Hematology		X		X
Hepatitis B and C[c]			X	
IMMUNOGENICITY				
[redacted]				
PHARMACOKINETIC ASSESSMENTS				
Pharmacokinetic Samples	X	X	X	X

EOS = end of study; **IP = investigational product; PCR = polymerase chain reaction**

[a] **This table applies for subjects who have completed the planned 52-week treatment period. Subjects are required to attend as many follow-up visits as necessary to ensure a minimum of 16 weeks of safety follow-up after the last administration of the investigational product.**

[b] **After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 9.2.3.1.1.3 for additional details.**

[c] For subjects who require monitoring, **PCR test to assess viral load should be performed at approximately every 3 months from baseline and up to a minimum of 16 weeks after the last administration of the investigational product**. See Section 6.2 criterion 208.

3. Introduction

3.1 Study Rationale

This is a phase 2b dose-ranging study to assess efficacy and safety of rozibafusp alfa (AMG 570) in subjects with active systemic lupus erythematosus (SLE).

This study will help determine if AMG 570 could be a useful therapeutic agent in the current treatment landscape where subjects have ongoing disease activity despite treatment with standard of care therapies.

Three dose levels of AMG 570 (70 mg **subcutaneous [**SC**] every 2 weeks [**Q2W**]**, 280 mg SC Q2W, and 420 mg SC Q2W) were selected based on **pharmacokinetic (**PK**)**/pharmacodynamic (PD) modeling and analysis of emerging PK, B cell activating factor (BAFF) inhibition (ie, % change in % naïve B-cells), and inducible co-stimulator ligand (ICOSL) % receptor occupancy (RO) data from previous studies (AMG 570 Investigator's Brochure **[IB]**). These dose regimens are proposed to promote characterization of exposure-response relationships in this phase 2b SLE study and inform dose selection for future studies.

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 [US], blacks and Hispanics) and women of childbearing potential (Rhaman and Isenberg, 2008; Kotzin, 1996). In the US, moderate to severe SLE is estimated to affect one-third of the more than 250,000 patients diagnosed with lupus. SLE disease activity 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. SLE can affect the skin (rash), musculoskeletal system (arthritis) nervous system (seizures, psychosis), lungs (pleuritis, pneumonitis), and the blood (venous or arterial thrombosis, anemia, thrombocytopenia, and leukopenia). In addition, approximately 65% of patients will develop lupus nephritis that can range from mild glomerulonephritis to severe diffuse proliferative glomerulonephritis (Adams et al, 2006).

Current treatment options include antimalarials, corticosteroids **(CS)**, and other immunomodulators/immunosuppressants, and few biologics (including Benlysta), which have limited efficacy and may have toxicities that impede a patient's ability to remain on therapy. Therefore, significant need exists for effective therapies with limited toxicities. SLE is both clinically and immunologically heterogenous; however, the presence of

class-switched, hypermutated immunoglobulin G (IgG) autoantibodies implicate immune dysregulation as a driving force for disease pathogenesis, with T cells playing a role in the development of autoantibody production by B cells.

3.2.2 Amgen Investigational Product Background: AMG 570

AMG 570 is a bispecific IgG2 antibody**-peptide conjugate** inhibiting both ICOSL and BAFF. AMG 570 contains 2 tandem copies of BAFF-binding peptides fused to the C-terminus of a fully human IgG2 against ICOSL. In terms of anti-BAFF effect, AMG 570 has similar binding affinity and cellular potency to relevant BAFF inhibitors. AMG 570 binds and inhibits cynomolgus monkey ICOSL and BAFF, but not rodent ICOSL. A mouse surrogate ICOSL/BAFF bispecific molecule showed dual-target inhibition in vivo and was more efficacious than single ICOSL or BAFF inhibitors in the mouse NZB/NZW lupus model (AMG 570 Investigator's Brochure). Thus, we hypothesize that targeting both ICOSL and BAFF by AMG 570 will achieve a large effect size in the treatment of autoantibody associated diseases, such as SLE.

3.3 Clinical Studies With AMG 570

3.3.1 First in Human (FIH) Study 20140322

In the first in human (FIH) study in healthy volunteers, a total of 56 subjects were enrolled and randomized to receive AMG 570 or placebo; 42 subjects received AMG 570 (6 per dosing cohort; dose range: 7 to 700 mg), and 14 subjects received placebo. Four subjects (7.1%, AMG 570 group) discontinued from the study; of these, 3 subjects (5.4%) were lost to follow-up and 1 subject (1.8%) withdrew consent. AMG 570 was generally well tolerated with most adverse events being mild in severity. One subject from the 7 mg cohort had a serious adverse event of injury, which was considered not related to investigational product. No subject had any clinically significant, life-threatening, or fatal adverse event. No dose limiting toxicities or withdrawals due to adverse events were reported.

The FIH study included 2 humoral immune status stopping rules that accounted for the potential of AMG 570 to decrease total circulating B cells and/or serum IgG levels. If a single subject in the FIH study satisfied the humoral immune status stopping rules, further studies with AMG 570 would shift from healthy volunteers to patients. No subject satisfied these rules during the course of the study.

3.3.1.1 FIH Study 20140322 – Clinical Pharmacokinetics

The PK of AMG 570 were assessed in the FIH study.

After a single SC dose, AMG 570 exposure was greater than dose proportional in the dose range of 7 to 700 mg. However, exposures across the dose range from 210 to 700 mg SC suggested that approximately dose-proportional exposure as assessed by maximum concentration (C_{max}) may be observed in the dose range of 210 to 700 mg.

3.3.1.2 FIH Study 20140322 – Clinical Pharmacodynamics

A validated, semi-quantitative flow cytometry assay was developed to monitor the PD properties of the constituent arms of the bispecific in whole blood specimens.

The effect of AMG 570 on ICOSL receptor occupancy was substantial with more than 90% receptor occupancy on total B cells at 8 days after dosing in 420 mg and 700 mg AMG 570 dose groups. A prominent effect of AMG 570 was observed on B cell populations, with a decreased percentage of naïve and increased percentage of memory B cells. No treatment effect was observed on serum IgG, IgM, natural killer cells, and T cells.

3.3.2 Amgen Study 20160344

The safety, tolerability, and PK of single doses of AMG 570 was evaluated in healthy Japanese subjects in Study 20160344. A total of 12 subjects were enrolled and randomized to receive a single dose of AMG 570 210 or 420 mg SC (6 subjects per cohort). One subject (8.3%, AMG 570 420 mg group) withdrew consent and discontinued from the study. AMG 570 was generally well tolerated with 2 adverse events being mild (grade 1) in severity and considered not related to investigational product. No subject had serious, life-threatening, or fatal adverse events.

Following a single SC dose of AMG 570 210 or 420 mg in healthy Japanese subjects, mean C_{max}, and AUC_{inf} increased 2.4- and 3.9-fold, respectively, for a 2-fold increase in dose.

Inducible co-stimulator ligand receptor occupancy was > 85% on total peripheral B cells at 8 days after dosing in both AMG 570 210 and 420 mg treatment groups. A prominent effect of AMG 570 was observed on B cell populations, with a reduction of naïve B cells and an increase in memory B cells.

One subject (8.3%) had pre-existing anti-AMG 570 antibodies at baseline and 11 subjects (91.7%) developed anti-AMG 570 antibodies after dosing; the effect of anti-AMG 570 antibodies on the PK after a single SC dose of AMG 570 could not be

determined. There was no association between AMG 570 binding antibodies and any adverse events.

3.3.3 Amgen Study 20150196

The safety, tolerability, and PK of multiple ascending doses of AMG 570 was evaluated in subjects with rheumatoid arthritis (RA) in Study 20150196. The study had 4 cohorts, each receiving 6 doses of AMG 570 ranging from 70 to 420 mg SC given **Q2W** based on cohort. A total of 32 subjects were planned (8 per cohort); 34 subjects were treated as 9 subjects were enrolled in both cohorts 1 and 4 (7 subjects received AMG 570 and 2 received placebo). There were no deaths or drug-related serious adverse events, dose-limiting toxicities, or withdrawals due to adverse events. In general, AMG 570 had an acceptable safety profile at the doses tested.

3.4 Toxicology

The AMG 570 safety profile was evaluated in 3- and 6-month Good Laboratory Practice (GLP) repeat-dose toxicology studies in the cynomolgus monkey as well as in several in vitro test systems. In both the 3-month toxicology study with an 8-month recovery (30, 100, and 200 mg/kg, 13 weekly SC injections) and 6-month study (100 and 200 mg/kg, 26 weekly SC injections), the no-observed-adverse effect-level (NOAEL) was 200 mg/kg. AMG 570 pharmacology-related effects (ie, decreased B cells, IgG, and lymphoid depletion of the lymphoid tissues) were observed at all dose levels. In the 3-month study, all changes were shown to be reversible within 8 months after the end of the dosing phase. Increased reticulocyte counts and subsequently increased red blood cell (RBC) mass were observed in a limited number of animals (4 animals in total; 1 animal at 100 mg/kg in the 3-month study and 1 and 2 animals at 100 and 200 mg/kg, respectively, in the 6-month study) but no adverse consequences were observed.

All the clinical dose levels in the ongoing and planned clinical studies are supported by adequate exposure margins based on the NOAEL (200 mg/kg) from the 3-and 6-month GLP repeat-dose toxicology studies in the cynomolgus monkey (NOAEL exposure in the monkey corresponded to ≥ 16-fold above exposures expected/observed at clinical doses). A detailed description of nonclinical safety studies is provided in the AMG 570 Investigator's Brochure.

3.5 Benefit/Risk Assessment

The following benefit-risk assessment supports the conduct of this clinical trial. Reference should be made to the AMG 570 Investigator's Brochure (IB) for further data on AMG 570.

3.5.1 Therapeutic Context

S**ystemic** L**upus** E**rythematosus** is a chronic autoimmune disease with no known cure and unpredictable disease flares that can lead to progressive disability, marked by moderate or severe exacerbations and sometimes fatal outcomes. Inflammation can arise in almost any major organ system of the body leading to manifestations such as rash, arthritis, bone tissue death, leukopenia, seizures, psychosis, pleuritis, pneumonitis, thromboses, anemia, nephritis and renal failure. Current treatment options include antimalarials, **CS**, immunomodulators, immunosuppressants, and few biologics (including Benlysta), these therapies have limited efficacy and may have toxicities that impede a patient's ability to remain on therapy. A substantial unmet medical need exists for these patients who have active disease despite SOC therapy.

3.5.2 Key Benefits

Phase 1 studies for AMG 570 have completed, and predicate evidence indicates potential biological and/or clinical benefits in lupus patients upon targeting either ICOSL or BAFF in isolation (Cheng et al, 2018; Zhang et al, 2018; Doria et al, 2018; Sullivan et al, 2016; Furie et al, 2011; Navarra et al, 2011; Chandran et al, 2007).

3.5.3 Key Risks

The safety, tolerability, and PK/PD of single ascending doses of AMG 570 were evaluated in the FIH Study 20140322 in healthy subjects. A total of 56 subjects received blinded investigational product at SC doses up to 700 mg. All subjects receiving dose levels up to 700 mg SC in the single ascending dose study demonstrated acceptable safety and tolerability with no drug-related severe, life-threatening, or fatal events reported. All adverse events were of mild to moderate severity. Safety, tolerability, and PK of multiple ascending doses of AMG 570 were evaluated in subjects with RA in Amgen Study 20150196. There were no deaths or drug-related serious adverse events, dose-limiting toxicities, or withdrawals due to adverse events**.** Adverse events occurring 2 or more times include: headache, arthralgia, pain in extremity, upper respiratory tract infection, dizziness, RA flare, and sciatica. All these events were mild or moderate. In general, AMG 570 was well tolerated at the doses tested.

An additional assessment of potential side effects of multiple doses of AMG 570 is based on the preclinical studies conducted to date and by observations of safety and tolerability of molecules that inhibit only ICOSL or BAFF. Summaries of findings from the nonclinical studies with AMG 570 can be found in the AMG 570 IB. No target organs beyond pharmacologic effects of AMG 570 were identified up to the high dose in the

GLP cynomolgus monkey toxicology study (200 mg/kg: 11 to 64.5 times higher than planned clinical doses [70 to 420 mg]).

Potential side effects of AMG 570 could also be related to the biological nature of the molecule and mode of administration.

Please refer to the AMG 570 IB, Section 7 for a description of these potential side effects.

4. Objectives, Endpoints and Hypothesis

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the efficacy of AMG 570 at week 52 as measured by the Systemic Lupus Erythematosus **(SLE)** Responder Index (SRI-4)	• SRI-4 response at week 52
The primary estimand is the difference in SRI-4 response between each AMG 570 dose group and placebo at week 52 for all subjects with SLE with inadequate response to SOC therapy who are randomized regardless of **investigational product** discontinuation; subjects using more than protocol-allowed therapies will be considered as non-responders.	
Secondary	
• Evaluate the efficacy of AMG 570 at week 24	• SRI-4 response at week 24 • **British Isles Lupus Assessment Group (**BILAG**)** based Combined Lupus Assessment (BICLA) response at week 24
• Evaluate the efficacy of AMG 570 at week 52	• Lupus Low Disease Activity State (LLDAS) response at week 52 • BICLA response at week 52
• Evaluate the efficacy of AMG 570 as measured by SRI-4 response with oral corticosteroid (OCS)-tapering	• SRI-4 response at week 52 with reduction of OCS to ≤ 7.5 mg/day by week 44 and sustained through week 52 in subjects with a baseline OCS dose ≥ 10 mg/day
• Evaluate the efficacy of AMG 570 on disease flares	• Annualized moderate and severe flare rate (as measured by SELENA-SLEDAI Flare Index) over 52 weeks • Annualized severe flare rate (as measured by SELENA-SLEDAI Flare Index) over 52 weeks • Annualized flare rate (as measured by BILAG score designation of “worse” or “new” resulting in a B score in ≥ 2 organs or an A score in ≥ 1 organ) over 52 weeks
• Evaluate the efficacy of AMG 570 on joints and skin	• Total tender and swollen joint count (limited to hands and wrists): ≥ 50% improvement from baseline at week

Objectives	Endpoints
	12, 24, 36, and 52 in subjects with ≥ 6 tender and swollen joints **in** hands and wrists at baseline • Cutaneous Lupus Erythematosus Area and Severity Index (CLASI) activity score: ≥ 50% improvement from baseline at week 12, 24, 36, and 52 in subjects with a CLASI activity score ≥ 8 at baseline
• Describe the efficacy of AMG 570 using patient reported outcomes	• Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a Instrument (PROMIS-Fatigue SF7A) score and change from baseline at week 12, 24, 36, 44, and 52 • Medical Outcomes Short Form 36 version 2 Questionnaire (SF-36v2) change from baseline **in the physical component** score**, mental component** score **individual domains of the Medical Outcomes Short Form 36 version 2 questionnaire (SF-36v2)** at week 12, 24, 36, 44, and 52 • Lupus **Quality of Life questionnaire (Lupus**QoL**)** score and change from baseline at week 12, 24, 36, 44, and 52 • Patient Global Assessment (PtGA) score and change from baseline at week 12, 24, 36, 44, and 52
• Characterize the safety of AMG 570	• Treatment-emergent adverse events • Serious adverse events • Clinically significant changes in laboratory values and vital signs
• To characterize the pharmacokinetics (PK) of AMG 570	• Trough serum concentrations and terminal elimination half-life of AMG 570

Objectives	Endpoints
Exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

4.2 Hypothesis

AMG 570 administered for 52 weeks will be well tolerated and have greater efficacy than placebo as measured by **Systemic Lupus Erythematosus Responder Index (**SRI-4**)** response at week 52 in subjects with active SLE and an inadequate response to SOC therapy.

5. Study Design

5.1 Overall Design

This is a Bayesian adaptive phase 2b, multi-center, double-blind, randomized, placebo-controlled, 52-week, dose-ranging study in subjects with active SLE and inadequate response to SOC therapies including **oral corticosteroids (**OCS**)**, immunosuppressants, and immunomodulators. Previous biologic use is allowed with an adequate washout period (see Exclusion Criterion 215).

Approximately 320 subjects will be enrolled and randomized to receive AMG 570 SC at 70 mg Q2W, 280 mg Q2W, 420 mg Q2W, or placebo. The randomization starts as 1:1:1:1 and then could be adapted at each interim analysis (IA) (if before full enrollment) based on the clinical efficacy (Response Adaptive Randomization [RAR]) for allocating more subjects to more efficacious doses and fewer subjects to less efficacious doses. The randomization allocation probability for placebo group will be kept constant at 25%. Randomization will be stratified by geographic region (North America + Western Europe vs rest of the world [ROW]) and screening **Hybrid Systemic Lupus Erythematosus Disease Activity Index (**hSLEDAI**)** score (≥ 10 or < 10).

Study duration for a single subject will be 52 weeks (treatment period) plus the screening period and safety follow-up period. Investigational product will be administered Q2W with the final dose at week 50. If a subject discontinues investigational product prior to completing week 52 visit, the subject will be encouraged to continue in the study and maintain the planned scheduled assessment for monthly efficacy and safety visits **through week 52** (Table 2-1). **Subjects are required to attend as many follow-up visits as necessary to ensure a minimum of 16 weeks of safety follow-up after the last administration of the investigational product. For subjects who discontinue investigational product prior to week 36, the safety follow-up visits will be included within the 52-week period and no additional safety follow-up visits will be required**. Immunogenicity [redacted] and PK samples should be collected at the first 4 visits after investigational product discontinuation.

Subjects will undergo a screening visit to confirm eligibility requirements. Baseline/day 1 visit should not occur prior to confirmation of subject's SLE-related eligibility by the adjudication team and must occur up to 33 days from the screening visit. At baseline/day 1 visit, prior to randomization, the subject must present with disease activity (defined by clinical hSLEDAI score ≥ 4) and stability and compliance with OCS and other immunosuppressant/immunomodulator doses (by reviewing medication history). Subjects may be randomized at any time after confirmation of all eligibility criteria, but the maximum time between initiation of screening and randomization is 33 days. Subjects who do not meet all the eligibility requirements at the baseline/day 1 visit will be considered screen failures. Subjects may be allowed to rescreen as detailed in Section 9.1.1.

After randomization, adjudication reviews will be completed throughout the study period on blinded endpoint data from enrollment to week 52 for all randomized subjects and for all visits. This includes review of all efficacy-related endpoint data.

Immunosuppressant/immunomodulator dose should remain stable through week 52. For OCS, initiation of, or temporary increases in OCS are allowed from weeks 0 to 8, provided that return to baseline dose occur within the subsequent 2 weeks, as outlined in Section 7.1.4.2. OCS can be tapered at the investigator's discretion but shall not be changed during the last 8 weeks (week 44 to 52) of the 52-week treatment period.

Subjects listed below will be allowed to continue the study but will be considered treatment failures for primary efficacy endpoint analyses for the subsequent time points. **These subjects will also be allowed to continue investigational product at the investigator's discretion, except subjects who initiate any immunosuppressant/immunomodulator listed in Section 7.1.7 (treatments a through i).**

- Subjects requiring initiation or increase in OCS dose > 5 mg/day (prednisone or equivalent), **or intramuscular (IM) CS or intravenous (IV) CS** at any time point during the study, subjects requiring initiation or increase in OCS dose ≤ 5 mg/day (prednisone or equivalent) after week 10, or subjects requiring initiation or increase in OCS dose ≤ 5 mg/day (prednisone or equivalent) from week 0 to week 8 who cannot return to their baseline dose within the following 2 weeks (Section 7.1.4.2).
- Subjects requiring either dose increases of the current immunosuppressants/immunomodulators or initiation of new immunosuppressant/immunomodulator(s) at any time point during the study (Section 7.1.7).

This study will utilize adaptive design elements based on the results of planned IAs:

- IAs will be conducted by an Independent Biostatistics Group (IBG) and will be reviewed by a Data Monitoring Committee (DMC), both external to Amgen. The study team, investigators and subjects will remain blinded to the results of the **IAs**.
- Adaptive randomization begins after a fixed allocation period. After each IA (if before full enrollment), the randomization probability for each of the 3 active doses may be changed based on clinical efficacy, while the randomization probability for placebo is kept constant, ie, 25%.
- Efficacy is assessed against predefined early stopping rules for futility from the second IA until before the last IA. If futility is triggered, the study could be terminated, eg, continued enrollment and follow-up activities for previously enrolled subjects would be stopped, etc.
- Efficacy is assessed against predefined rules for administrative success only at the last IA. If administrative success is determined, downstream activities may be planned/initiated (eg, a phase 3 study), but the execution of this study would not be stopped or altered.

5.2 Number of Subjects

Approximately 320 subjects will be enrolled in the study; however, the actual sample size could be smaller as the study can be stopped earlier if futility is reached at IAs.

Participants 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 are withdrawn or removed from treatment or the study will not be replaced.

5.2.2 Number of Sites

Approximately 150 investigative sites globally will be included in the study. Sites that do not enroll subjects within 6 months of site initiation may be considered for closure.

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), for the purposes of conducting the primary analysis, 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

Study duration for a single subject will be 52 weeks plus the screening period (up to 33 calendar days) and safety follow-up period (**a minimum of 16 weeks after the last administration of the investigational product).**

If a subject discontinues investigational product prior to completing week 52 visit, the subject will be encouraged to continue in the study and maintain the planned scheduled assessment for monthly efficacy and safety visits through week 52 (Table 2-1**).**

For subjects who discontinue investigational product prior to or at week 36, the safety follow-up visits will be included within the 52-week period and no additional safety follow-up visits will be required. Subjects who discontinue investigational product after week 36 are required to attend as many follow-up visits as necessary to ensure a minimum of 16 weeks of safety follow-up period after the last administration of the investigational product (Table 2-2**).**

Subjects have completed the study when: 1) have completed 52-week treatment period regardless of investigational product compliance, and 2) have completed a minimum of 16 weeks of safety follow-up after the last administration of the investigational product.

5.4 Justification for Investigational Product Dose

Three dose levels of AMG 570 (ie, 70, 280, and 420 mg) were chosen for the study. Preclinical and clinical data supporting the safety of a 420 mg SC Q2W dose are as follows: the NOAEL from nonclinical 6-month toxicology studies of 200 mg/kg SC weekly, corresponding to a maximum concentration (C_{max}) of 2490 μg/mL, and area under the curve from time 0 to 7 days (AUC_{0-7d}) of 13800 μg•day/mL. These exposures are 16-fold and 23-fold higher than the predicted steady-state mean C_{max} and AUC_{0-14d}, in humans at the 420 mg SC Q2W dose. Predicted steady-state AUC_{0-14d} from the 420 mg SC Q2W dosing regimen is also anticipated to be within the range of the exposures observed in previous AMG 570 clinical studies. Multiple doses up to 420 mg are expected to be well tolerated in subjects with moderate to severe SLE as it was

shown in healthy subjects following single dose administration up to 700 mg SC. Multiple dose administration up to 420 mg Q2W X 6 (Study 20150196) in subjects with RA was also well tolerated. Exposure ($AUC_{0\text{-}inf}$) after a single dose of 700 mg was 35% higher than the projected steady-state exposure ($AUC_{0\text{-}14d}$) of 420 mg Q2W at steady-state. Thus, the highest selected dose is predicted to result in exposures that are 16- to 23-fold lower than those achieved at the NOAEL dose in preclinical toxicology studies and are lower than what was achieved with the 700 mg SC dose in humans, which was generally well tolerated.

The 3 dose levels were also chosen with the intent to characterize the dose-response and exposure-response relationships and to inform dose selection for the phase 3 program. The dose selection strategy integrates the 2 targets of AMG 570. Impact of BAFF inhibition on naïve B cell reduction and efficacy in the SLE patient population was previously demonstrated for BAFF inhibitors (eg, Benlysta) (Arthritis & Rheumatism, 2009). Impact of inhibition of ICOSL was previously demonstrated for AMG 557 (Sullivan et al, 2016), where maximal inhibition of the anti-KLH IgG response occurred at doses associated with ICOSL saturation.

The dosing regimens for this phase 2b study were selected using PK/PD modeling and simulation based on available data from the single ascending dose study in healthy subjects (Study 20140322) and multiple ascending dose study in RA subjects (Study 20150196).

The PK/PD analysis was based on biologic changes consistent with BAFF inhibition (ie, % change in % naïve B cells) and modeling of the AMG 570 Exposure-ICOSL % receptor occupancy relationship.

The highest planned dose of 420 mg Q2W was chosen to evaluate attainment of maximal coverage of both targets. This dose is predicted to achieve maximal reduction in % change naïve B cells and achieve maximal saturation of ICOSL (mean percent receptor occupancy of > 90%) in ~98% of simulated subjects at steady-state trough.

The lowest planned dose of 70 mg Q2W will provide additional dose-ranging information for characterization of the dose-response and exposure-response relationships. This dose is predicted to achieve maximal reduction in % change naïve B cells and achieve minimal saturation of ICOSL (mean percent receptor occupancy of 50% to 90% in ~80% of simulated subjects) at steady-state trough. Efficacy at this dose may also allow comparison of AMG 570 to the efficacy associated with BAFF inhibitors (ie, Benlysta).

The dose of 280 mg SC Q2W is predicted to achieve maximal reduction in naïve B cells and near maximal ICOSL coverage (mean percent receptor occupancy of > 90% in ~90% of simulated subjects at steady-state trough).

Overall, the safety of the selected doses is supported by the clinical and preclinical data, and the 3 doses have been selected to evaluate dose-response and exposure-response relationships.

5.5 Patient Input on Study Design

Patient input was obtained for this study in various international regions. Patients were able to understand and comment on the requirements for study participation.

6. Study Population

Screening: 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 may be completed and updated via an Interactive Response Technology (IRT) system. Eligibility criteria will be evaluated at screening visit and at baseline/day 1 visit, prior to randomization.

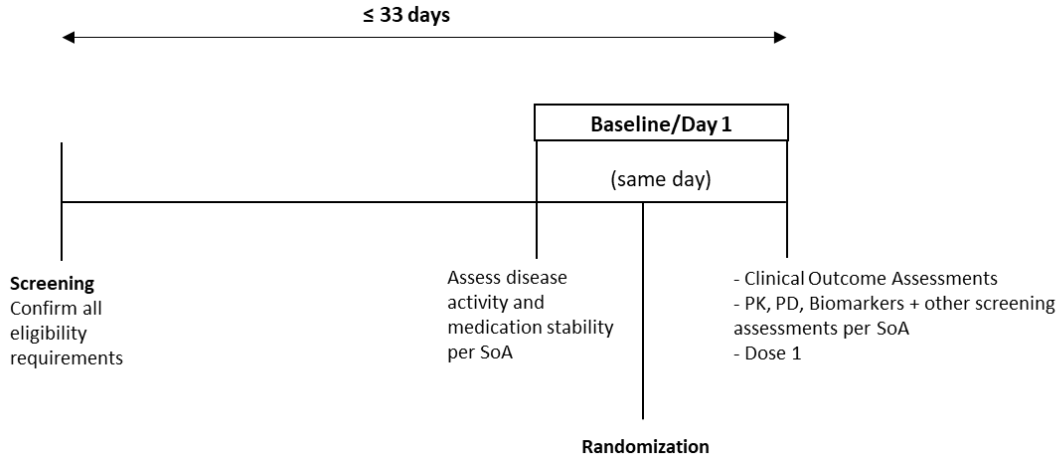
The screening visit will confirm all eligibility requirements described in Section 6.1 and 6.2 and Table 2-1. All SLE-related screening criteria will be reviewed by the adjudication team. The site will be notified by electronic communication of the results of this review and baseline/visit 1 should not occur prior to this notification. Subjects who do not meet the eligibility criteria will be considered screen fails but may be eligible for rescreening as described in Section 9.1.1.

The baseline/day 1 visit will occur up to 33 calendar days following the screening visit (it can be earlier if all eligibility requirements for screening visit are met). Baseline/day 1 visit will confirm eligibility requirements prior to randomization, as described in Section 6.3. Subject who meet all eligibility criteria may proceed to randomization and dosing. Subjects who do not meet criteria may be eligible for rescreening as described in Section 9.1.1.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 12.3).

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

Figure 6-1. Screening and Enrollment



PD = pharmacodynamic; PK = pharmacokinetic; SLE = systemic lupus erythematosus

6.1 Inclusion Criteria Screening Visit

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

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

102 Age ≥ 18 years to ≤ 75 years at screening visit.

103 Fulfills classification criteria for SLE according to the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for SLE (Aringer et al, 2019), with antinuclear antibody ≥ 1:80 by immunofluorescence on Hep-2 cells being present at screening.

104 Hybrid SLEDAI score ≥ 6 points with a "Clinical" hSLEDAI score ≥ 4 points.

The "Clinical" hSLEDAI is the hSLEDAI assessment score without the inclusion of points attributable to laboratory results, including urine or immunologic parameters.

Additional protocol-specific rules are applied at screening and throughout the study, as follows:

- Arthritis: Arthritis (at least 3 tender and swollen joints) must involve joints in the hands or wrists for the hSLEDAI scoring.
- Alopecia: Subjects should have hair loss without scarring; should neither have alopecia areata nor androgenic alopecia; and should have a CLASI activity score for alopecia ≥ 2.
- Oral ulcers: Ulcers location and appearance must be documented by the investigator.
- Scleritis and Episcleritis: the presence of stable SLE-related scleritis and episcleritis (ie, that will likely not require initiation/increase in immunosuppressants/immunomodulators as outlined in the

inclusion/exclusion criteria) must be documented by an ophthalmologist and other causes excluded.

- Renal: subjects with urine protein/creatinine ratio < 3000 mg/g (or equivalent method) in a clear catch spot urine sample can enroll and be scored in the hSLEDAI, provided the subject has a clinical hSLEDAI ≥ 4 and did not receive induction treatment for nephritis within the last year.
- Pleurisy and Pericarditis: symptoms of pleurisy and pericarditis must be accompanied by objective findings to be scored in the hSLEDAI.

105 Unless there is a documented intolerance**, subjects m**ust be taking:

- **Only** 1 of the following SLE treatments: anti-malarial (hydroxychloroquine, chloroquine, or quinacrine), azathioprine, methotrexate, **leflunomide,** mycophenolate mofetil/acid mycophenolic, or dapsone.

  OR

- 2 of the above-mentioned SLE treatments in which 1 must be **anti-malarial** (hydroxychloroquine, chloroquine, or quinacrine).

Treatment should be taken for ≥ 12 weeks prior to screening and must be a stable dose for ≥ 8 weeks prior to screening.

106 For subjects taking OCS, dose must be ≤ 20 mg/day of prednisone or OCS equivalent, and the dose must be stable at baseline visit for ≥ 2 weeks prior to screening visit.

6.2 Exclusion Criteria Screening Visit

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

Disease Related

201 Urine protein creatinine ratio ≥ 3000 mg/g (or equivalent) at screening or induction therapy for lupus nephritis within 1 year prior to screening visit.

202 Active CNS lupus within 1 year prior to screening including, but not limited to, aseptic meningitis, ataxia, CNS vasculitis, cranial neuropathy, demyelinating syndrome, optic neuritis, psychosis, seizures, or transverse myelitis.

Other Medical Conditions

203 Diagnosis of any inflammatory joint or skin disease other than SLE (confirmed accurate by the PI) currently present or within 1 year prior to screening which would interfere with SLE disease assessment based on investigator judgment.

204 Any disease other than SLE that has required treatment with oral or parenteral **CS** for > 2 weeks within 6 weeks prior to screening.

205 Active infection (including chronic or localized infections), **OR infection** for which anti-infectives were **initiated** within 4 weeks prior to screening OR presence of serious infection, defined as requiring hospitalization or **IV** anti-infectives within 8 weeks prior to screening.

206 Active tuberculosis or latent tuberculosis with no documented past history of adequate treatment per local standard of care.

207 Positive test for tuberculosis during screening defined as: either positive or indeterminate QuantiFERON®-TB OR T-spot test OR positive purified protein derivative (PPD) (≥ 5 mm of induration at 48 to 72 hours after test is placed).

- Subjects with a positive PPD and a history of Bacillus Calmette-Guérin vaccination are allowed to enroll with a negative QuantiFERON®-TB or T-Spot test.
- Indeterminate QuantiFERON®-TB or T-spot test can be repeated once, based on investigator judgment. Subjects can enroll if second result is negative. Subjects with persistent indeterminate or positive test results should proceed as below.
- Subjects with a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or a positive or indeterminate QuantiFERON®-TB or T-Spot test (including repeated results when performed) are allowed to enroll if they meet ALL the following criteria at screening:
  - no symptoms per tuberculosis worksheet provided by Amgen
  - documented history of adequate TB treatment or prophylactic treatment for latent TB (completed per local standard of care prior to the start of investigational product)
  - no known exposure to a case of active tuberculosis after most recent treatment/prophylaxis
  - chest X-ray with no new radiographic findings suggestive of active TB (to be read by local facility)

  Note: 1) these tests do not need to be repeated at the time of rescreening, unless rescreening occurs ≥ 12 months from screening visit or subject's medical/epidemiologic history suggests newly acquired infection or recent contact with TB cases and 2) repeat testing of an indeterminate QuantiFERON test using the T-spot test may be performed.

208 Positive for hepatitis B surface antigen (HBsAg); or positive for hepatitis B core antibody (HBcAb) in the presence of detectable viral DNA in peripheral blood, assessed by polymerase chain reaction (PCR). Subjects positive for HBcAb without detectable viral DNA by PCR are allowed to enroll, provided the subject undergoes monitoring of viral DNA by PCR at **approximately** every 3 months during the treatment period, up to **a minimum of** 16 weeks after **last administration of** the **investigational product**. If viral DNA becomes detectable during the study period, the subject should be evaluated by an hepatologist before stopping the treatment to evaluate the need to start specific hepatitis B treatment before investigational product discontinuation. A history of hepatitis B vaccination without history of hepatitis B infection (ie, positive hepatitis B surface antibody (HBsAb), negative HBsAg and negative HBcAb) is allowed.

Positive for hepatitis C antibody in the presence of detectable viral ribonucleic acid (RNA) in peripheral blood, assessed by PCR. Subjects positive for hepatitis C antibody without detectable viral RNA by PCR are allowed to enroll, provided the subjects undergo monitoring of viral RNA by PCR at **approximately** every 3 months during treatment period up to **a minimum of** 16 weeks after **last administration of** the **investigational product**. If viral RNA become detectable during the study period, the subject should be evaluated by an hepatologist before stopping the treatment to evaluate the need to start specific hepatitis C treatment before investigational product discontinuation.

Note: these tests do not need to be repeated at the time of rescreening, unless rescreening occurs ≥ 12 months from screening or there is evidence or suspicion of recent infection.

209 Known history of HIV or positive serology for HIV antibodies at screening.

Note: these tests do not need to be repeated at the time of rescreening, unless rescreening occurs ≥ 12 months from screening or there is evidence or suspicion of recent infection.

210 Presence of 1 or more significant concurrent medical conditions per investigator judgment, including but not limited to the following:

- poorly controlled diabetes or hypertension
- symptomatic heart failure (New York Heart Association class III or IV)
- myocardial infarction or unstable angina pectoris within the past 12 months prior to screening
- severe chronic pulmonary disease requiring oxygen therapy
- multiple sclerosis or any other demyelinating disease
- major chronic inflammatory disease or connective tissue disease other than SLE (eg, RA, Primary Sjogren Syndrome, Mixed Connective Tissue Disease)

Note: Subjects with positive antiphospholipid antibodies or diagnosis of antiphospholipid antibody syndrome according to the revised Sapporo classification criteria (Miyakis et al, 2006) can enroll in the study provided they have no current or past history of thrombotic events and meet all the other eligibility criteria.

211 Any history of malignancy with the following exceptions:

- resolved non-melanoma skin cancers > 5 years prior to screening
- resolved cervical carcinoma > 5 years prior to screening
- resolved malignant colon polyps > 5 years prior to screening

Prior/Concomitant Therapy

212 Currently receiving or had treatment with: cyclophosphamide, chlorambucil, nitrogen mustard, or any other alkylating agent within 6 months prior to

screening; sirolimus or oral calcineurin inhibitors (eg, cyclosporine, tacrolimus, voclosporin) **or thalidomide** within 4 weeks prior screening.

213 Currently receiving or had treatment with a **Janus kinase (**JAK**)** inhibitor within **1** month prior to screening.

214 Currently receiving or had treatment with an immune checkpoint inhibitor (eg, PD-1 inhibitor, PD-L1 inhibitor, CTLA-4 inhibitor).

Note: Abatacept is not considered a CTLA-4 inhibitor and is referred to below.

215 Current or previous treatment with a biologic agent **with immunosuppressive/immunomodulatory activity** for SLE or other conditions as follows: rituximab within 6 months prior to screening; **abatacept,** belimumab**,** and anifrolumab within the past 3 months prior to screening; other biologics within less than 5 drug half-lives **or within the period of pharmacodynamic activity, when relevant,** prior to screening.

216 Subjects who have received intra-articular, intra-lesional, or systemic corticosteroid injections within 6 weeks prior to screening.

217 Subjects who have received live vaccines within 5 weeks prior to screening, or plan to receive live vaccines during the treatment period and up to 16 weeks after **last administration** of the **investigational product.**

Prior/Concurrent Clinical Study Experience

218 Currently receiving treatment in another investigational device or drug study.

219 Ending a treatment with an investigational drug or investigational device less than 5 **drug** half-lives from the last dose of the investigational **product or within the period of its pharmacodynamic activity when relevant**, at screening.

220 Subject previously randomized in this study.

Diagnostic Assessments

221 Presence of laboratory abnormalities at screening including the following:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x upper limit of normal (ULN)
- Serum total bilirubin (TBL) ≥ 1.2 mg/dL (≥ 26 μmol/L) **except for Gilbert's Syndrome**
- Hemoglobin < 8 g/dL (< 80 g/L)
- Platelet count < 75,000/mm^3 (75 x 10^9/L)
- White blood cell count < 2000 cells/mm^3 (2 x 10^9/L)
- Absolute neutrophil count (ANC) < 1,000/mm^3 (1 x 10^9/L)
- Calculated glomerular filtration rate of ≤ 30 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula

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

Other Exclusions

223 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for at least 10 additional weeks after the last dose of investigational product.

224 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for at least 10 additional weeks after the last dose of investigational product administration. Refer to Section 12.5 for additional contraceptive information.

225 Female subjects of childbearing potential with a positive pregnancy test (serum pregnancy test **required** at screening**,** and urine pregnancy test **required** at day 1 visit).

226 Subject has known sensitivity to any of the products to be administered during dosing.

227 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.

228 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 Central Review Team would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

6.3 Inclusion Criteria Baseline/Day 1 Visit

Baseline/day 1 visit should occur after confirmation of SLE-related eligibility by the adjudication team and up to 33 days after screening visit. At baseline/day 1 visit, the following 2 criteria should be assessed prior to randomization:

107 Stability of SLE treatments: OCS and other immunosuppressants/ immunomodulators doses must be stable since screening visit, by reviewing subject's medication history.

108 Disease activity: active disease as indicated by clinical hSLEDAI score ≥ 4 must be observed (clinical hSLEDAI score is the hSLEDAI assessment score without the inclusion of points attributable to laboratory results).

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 as applicable (see Section 12.3).

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 and all eligibility criteria (from screening visit and baseline/day 1 visit) are met. The investigator is to document this decision and date, in the subject's medical record and in the enrollment case report form (CRF). At baseline/day 1 visit, if the subject meets all eligibility criteria, he/she is subsequently enrolled and randomized to a treatment regimen. Subjects who meet screening visit eligibility but do not meet baseline/day 1 visit eligibility criteria are considered screen fails. Subjects may rescreen up to 2 times, as described in Section 9.1.1.

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.

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, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 additional times. Refer to Section 9.1.1.

7. Treatments

Investigational product 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 7.1.1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

AMG 570 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical investigational product distribution procedures. AMG 570 is a clear colorless sterile solution which will be packaged in open-label 5 mL glass vials containing 70 mg/ml of AMG 570 formulated with [redacted] Placebo will be presented in identical containers and stored/packaged the same as AMG 570, but will not contain AMG 570 protein. All AMG 570 and placebo will be shipped to the study site and should be stored the same as AMG 570 at 2°C to 8°C with limited exposure to light.

For more information regarding investigational product handling and preparation please see the study-specific IPIM which is provided as a separate document.

Table 7-1. Investigational Products

Investigational Product Name	Amgen Investigational Product: AMG 570[a]	Placebo
Dosage Formulation	Clear colorless sterile solution in 5 mL glass vials containing 70 mg/mL of AMG 570	Placebo will be presented in identical containers, and stored/packaged the same as AMG 570
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	70 mg/Q2W 280 mg/Q2W 420 mg/Q2W	
Route of Administration	SC injection	
Accountability	**T**otal volume of preparation, quantity administered start date, start time, and box number of AMG 570 is to be recorded on each subject's CRF.	
Dosing Instructions	PI or designee will administer product in subject's abdomen. Dosing must be administered on day of scheduled visit after all clinical assessments have been completed. No dose adjustments for weight or restrictions with food intake are required.	

CRF = Case Report Form; PI = Principal Investigator; SC = subcutaneous; Q2W = every 2 weeks
[a]AMG 570 will be manufactured and packaged by Amgen and distributed using Amgen clinical investigational product distribution procedures.

7.1.2 Non-investigational Products

No non-investigational products will be used.

7.1.3 Medical Devices

There are no investigational medical devices used in this study.

Non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational, non-Amgen 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 Therapies

7.1.4.1 Immunosuppressants/Immunomodulators

Subjects should receive stable doses of immunomodulators and/or immunosuppressants agents from ≥ 8 weeks prior to screening through week 52. If a subject requires a higher dose of an immunosuppressant/immunomodulator or requires a new immunosuppressant/immunomodulator at any time during the study period (other than CS, see below), the subject may continue the study but will be considered treatment **failures** for **primary efficacy endpoint** analyses **for the subsequent time points. These subjects will also be allowed to continue investigational product at the investigator's discretion, except subjects who initiate any immunosuppressant/immunomodulator listed in Section 7.1.7 (treatments a through i).**

Subjects may reduce dosage in immunomodulators and/or immunosuppressants if the subject develops unacceptable side effects or abnormal laboratory values attributable to these medications.

7.1.4.2 Oral, Intramuscular, and Intravenous Corticosteroids

Initiation or temporary increases in the OCS dosage are not encouraged but are allowed if initiated at any time between weeks 0 to 8 with a return to baseline dose within the subsequent 2 weeks. In such cases, initiation or temporary increase of OCS is limited to a dose ≤ 5 mg/day of prednisone (or equivalent). Subjects who require higher dose increase **of OCS** (> 5 mg/day of prednisone or equivalent**), or IM CS or IV CS,** or **those who** cannot return to baseline dose within the following 2 weeks or subjects who require initiation or CS dose increase at any time point after week 10 can continue the study **or**

investigational product at the investigator's discretion but will be considered treatment failures for the primary efficacy endpoint.

Subjects may begin tapering OCS up to the week 44 assessment with initiation of tapering based upon clinical judgment of the treating physician. The tapering schedule should be directed at the discretion of the investigator but should generally not be tapered more than 10% to 20% of the prior dose per week. Between weeks 44 and 52, the OCS dosing should again remain stable.

7.1.4.3 Topical Corticosteroids and Topical Calcineurin Inhibitors

Subjects who are using topical **CS** or topical calcineurin inhibitors must remain on a stable regimen but may discontinue topical corticosteroids at any time if clinically indicated.

7.1.4.4 Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Other Analgesic Therapies

Subjects taking non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesic therapies should remain on stable dose from day 1 through week 52. NSAIDs or other analgesic therapies used for SLE disease activity should be held for 24 hours prior to the scheduled monthly efficacy assessments. Subjects can return to their regular doses immediately after the clinical visit is complete. Discontinuation or reduction of NSAIDs or other analgesic therapy dose during the study is allowed based on the investigator's judgment. Initiation or increases in the NSAIDs or other analgesic therapy dose during the study are allowed if: 1) not initiated within 24 hours of the scheduled monthly efficacy assessments**,** 2) the subject returns to baseline dose within the subsequent 2 weeks, and 3) it is not within 2 weeks prior to the week 52 visit.

7.1.4.5 Anti-proteinuria Agents

Subjects with SLE-related proteinuria taking anti-proteinuria agents (eg, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors), should remain on stable dose through week 52. Discontinuation or dose reduction of anti-proteinuria agents during the study is allowed in case of intolerance or toxicity. Initiation or dose increase of anti-proteinuria agents (eg, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors) for the purpose of SLE-related proteinuria during the study should be avoided.

7.1.5 Other Treatment Procedures

7.1.5.1 Home Health Care Visits

Section 7.1.5.1 is not applicable for participating sites in Bulgaria.

If permitted by national and/or local regulations, the investigator may utilize a qualified home health care service provider, selected and approved by the sponsor, for investigational product administration. This service can be offered to subjects that have not experienced adverse events considered to be related to investigational product that in the opinion of the investigator may pose a risk for home health care administration of investigational product. The study may include up to 8 home visits, including weeks 22, 26, 30, 34, 38, 42, 46, and 50. [redacted]. In addition to administration of investigational product, safety assessments including vital signs, adverse events, serious adverse events, and concomitant medications review will be collected.

Home health care staff must be included on the study delegation log (authorized by the investigator) before any study-related tasks to be conducted by each home health care provider are started. In addition, study-specific training including requirements for recording source documentation for the home health care provider, must be completed before they conduct any study-related tasks.

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

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

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**, combination product,** or device after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors **or** partners for whom Amgen manufactures the material. **This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.** This includes AMG 570/placebo provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product 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

Subjects who are receiving treatments listed below are allowed to remain in the study at the investigator's discretion. Subjects are also allowed to continue investigational product at the investigator's discretion except those who initiate any treatment listed below from a through i:

a. investigational therapies or commercially available biologic agents **with immunosuppressive/immunomodulatory activity** for SLE or other conditions (eg, rituximab or belimumab)
b. cytotoxic agents including: chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents
c. **thalidomide**
d. sirolimus
e. oral calcineurin inhibitors (eg, tacrolimus, cyclosporine, etc.)
f. T cell depleting agents (eg, antithymocyte globulin, Campath)
g. recombinant IL-2 (eg, Proleukin)
h. **JAK inhibitors**
i. **live vaccines**
j. intra-articular, **IM,** or **IV CS**, including adrenocorticotropic hormone
k. intra-articular hyaluronic acid injections

7.2 Method of Treatment Assignment

Subjects who meet all eligibility criteria will be randomized to receive AMG 570 at 70 mg Q2W, 280 mg Q2W, 420 mg Q2W, or placebo in a double-blind manner. The randomization starts as 1:1:1:1 and then could be adapted at each IA (if before full enrollment) based on the clinical efficacy (RAR) for allocating more subjects to more efficacious doses and fewer subjects to less efficacious doses. The randomization allocation probability for placebo group will be kept constant at 25%. The randomization will be stratified by geographic region (North America + Western Europe vs ROW) and screening hSLEDAI score (≥ 10 or < 10).

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 and on the enrollment CRF.

7.3 Blinding

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

7.3.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager be notified before the blind is broken unless the investigator believes that identification of the investigational product is required for a medical emergency. If this is not possible, 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. Continuation of such subjects in the study should be discussed with the medical monitor.

7.3.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information is not to be distributed to the study team, investigators or subjects prior to the study being formally unblinded which will occur at the final analysis except as specified (eg, Section 7.3.2). Otherwise, if unblinding occurs, only the subject and investigators will have access to what investigational product treatment was received and Amgen will not have access to this information.

Individual subject treatment assignments will be maintained by the IRT System. Any unplanned unblinding occurring during the study period will be documented and reported in the final clinical study report. Staff from Clinical Supply Chain, Biological Sample Management, PK and Drug Metabolism, Clinical Pharmacology Modelling and Simulation, Clinical Immunology, Department of Molecular Sciences and Computational Biology, Safety, internal team, and Global Biostatistical Science departments who are responsible for tracking, assaying, or analyzing biological samples during the conduct of this study are considered to be unblinded to the treatment assignments in this study. These individuals will not have access to subject level clinical data apart from the samples they are assaying and analyzing during the course of the study. If exposure-response analysis is performed, the exposure-response analysis team, including Clinical Pharmacology Modeling and Simulation (CPMS) and Global Biostatistics Sciences, who are independent of the study team, may be unblinded. If needed by the Development/Therapeutic Area (TA) Head to make decisions after receiving DMC recommendations at IAs, pre-specified independent biostatistician(s),

programmer(s), and/or CPMS scientist(s) outside the study team may be unblinded to carry out ad-hoc analyses as requested by the Development/TA Head at IAs (details will be specified in data access plan for IA).

7.3.3 Unblinding Procedure For Investigators

A subject's treatment assignment must only be unblinded when this knowledge is essential for management of the subject. Before unblinding, the investigator (or site) should contact Amgen. In the interest of subject safety, where this is not possible, the investigator must contact Amgen within 1 working day of the unblinding event. The actual treatment assignment must only be shared to those who require it for treatment of the subject and should not be recorded in the CRF. The IRT system will assign each subject, at each dispensing visit, with individually numbered Investigational Product containers. This unique number will form the basis of the unblinding information. For unblinding, only authorized staff assigned with access to the unblinding module in the IRT can obtain unblinding information. For further details on access and unblinding, refer to the IRT Manual.

Contact details for emergency unblinding:

Amgen, Inc.
Address: One Amgen Center Drive
Thousand Oaks, CA 91320, USA
Telephone: +1 (805) 447-1000

7.4 Dose Modification

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

All subjects will receive a fixed dose of the investigational product (AMG 570/placebo). No dose adjustments will be allowed.

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

7.4.2.1 Amgen Investigational Product: AMG 570 or Placebo

No dose adjustments will be allowed.

7.4.2.2 Non-Amgen Non-Investigational Product: SLE Standard of Care Therapy and Oral Corticosteroids

The reason for dose change of OCS (Section 7.1.4.2) and/or other medications including for SLE SOC therapies (Section 7.1.4; **anti-malarials,** azathioprine, methotrexate, **leflunomide**, mycophenolate mofetil, or dapsone) is to be recorded on each subject's CRF(s).

7.4.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 12.7 for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*. This will be used for stopping and rechallenge with the agent.

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 26 doses of investigational product (AMG 570 or placebo) at the research facility or via home health care visits, administered by qualified study personnel for the duration of the study. The investigational product will be administered Q2W and dosing should occur within a visit window of ± 3 business days from the scheduled dosing date. There should also be a minimum of 11 days between administrations of investigational product. If any scheduled dose after study day 1 is delayed 7 or more calendar days from the scheduled visit date, this will be considered a missed dose and recorded as such on the CRF. The next dose is to be given on the next scheduled visit date (based on study day 1). Subjects will be observed for at least 30 minutes following dose administration. Vital signs, adverse events, serious adverse events, concomitant medications and efficacy assessments will be obtained prior to administration of the investigational product.

7.7 Treatment of Overdose

The effects of overdose of this product are not known.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken/used from time of initial diagnosis with SLE through the date of randomization will be collected. For prior therapies, collect therapy name, indication, dose, unit, frequency, 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 therapies are to be collected from randomization through the end of the safety follow-up period. For concomitant therapies, collect therapy name, indication,

dose, unit, frequency, start date, and stop date. Guidelines for immunomodulators, immunosuppressants, and OCS are provided in Section 7.1.4.1 through Section 7.1.4.5.

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, and 8.2.1.

8.1 Discontinuation of Investigational Product

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other 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 therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1 and 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 and adverse events, as applicable and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or therapies or procedures should not be automatically removed from the study and will be encouraged to maintain the planned scheduled assessments for monthly efficacy and safety visits (Table 2-1 and Table 2-2) to allow safety surveillance and collection of outcome data up to week 52 or for a minimum of 16 weeks after the last dose of investigational product (see Section 9.1.2 for additional details).

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.3.

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

- Decision by Sponsor

- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Pregnancy
- Disease flare

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 Section 12.6 for further details). Refer to the Schedule of Activities (Section 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 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 (Section 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 investigational product.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 2), 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 33 calendar days.

All eligibility evaluations (at screening visit and baseline/day 1 visits, prior to randomization) must be completed to confirm that potential subjects meet all eligibility criteria (Section 6). The investigator will maintain a screening log to record details of all subjects screened, to confirm eligibility or record reasons for screening failure (see Section 6.5), as applicable. If a lab retest is required, the sponsor should approve prior to being retested.

A subject is considered enrolled when the investigator decides and all eligibility criteria (from screening visit and baseline/day 1 visit) are met. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment CRF. At baseline/day 1 visit, if the subject meets all eligibility criteria, he/she is subsequently enrolled and randomized to a treatment regimen.

If a subject has not met all eligibility criteria either during or at the end of the screening period (maximum 33 days), the subject will be registered in IRT as a screen fail. Subjects should always complete the 33-day screening period before being considered for re-screening. At that point, subjects may be rescreened, as follows:

- Subjects who do not meet the hSLEDAI criteria (total hSLEDAI score ≥ 6 at screening visit or clinical hSLEDAI score ≥ 4 at baseline/day 1 visit) must wait at least 2 weeks before rescreening.
- Subjects who have not maintained stable OCS dosing at day 1 will be required to wait at least 2 weeks prior to rescreening (Section 6.1).
- Subjects who have not maintained stable immunosuppressant/immunomodulatory dosing at day 1 will be required to wait at least 8 weeks prior to rescreening (Section 6.1).
- Subjects who met eligibility criteria but were not able to enroll within the screening period (within the 33 days), can rescreen immediately.

Once the subject is registered as rescreened, a new 33-day screening window will begin. All procedures noted in Section 6, including the informed consent and all laboratory parameters (Section 9.2.4) must be repeated with the following exception:

- tuberculosis screening tests (QuantiFERON®-T, T-spot test OR PPD), serologies for hepatitis B virus, hepatitis C virus and HIV may not be repeated provided that rescreening occurs $\leq$ 12 months of screening visit **(where those test results were negative)** and there is no patient's medical/epidemiological history suggestive of infection or recent exposure to cases of infection.

Screen fail subjects may be eligible for re-screening up to 2 times.

9.1.2 Treatment Period

The 52-week treatment period is the study period following randomization to the planned week 52 visit (regardless of investigational product compliance).

Visits will occur per the Schedule of Activities (Section 2.2). On-study visits may be completed within ± 3 business days of the scheduled visits. 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. The investigational product is to be administered following the completion of all other study required procedures for that visit.

9.1.3 Safety Follow-up

Following **last administration of** the i**nvestigational product**, a minimum of **16-weeks of safety follow-up assessments is required to ensure safety surveillance of subjects in the study.**

For subjects who discontinue investigational product prior to or at week 36, the safety follow-up visits will be included within the 52-week period and no additional safety follow-up visits will be required (Table 2-1**). Subjects who discontinue investigational product after week 36 are required to attend as many follow-up visits as necessary to ensure a minimum of 16 weeks of safety follow-up period after the last administration of the investigational product (**Table 2-2**).**

[redacted] **and PK samples should be collected during the first 4 safety follow-up visits after last administration of the investigational product.**

Subjects who are unwilling or unable to complete the follow-up visits as scheduled will be contacted by phone and may be requested to provide documentation from their primary provider.

9.1.4 Long-term Follow-up

Not applicable to this study.

9.1.5 End of Study

9.1.5.1 End of Study for Individual Subject

The end of study for an individual subject is defined as the last day the protocol-specific procedures are conducted for an individual subject. **An individual subject has completed the study when: 1) has completed 52-week treatment period regardless of investigational product compliance, and 2) has completed a minimum of 16 weeks of safety follow-up after the last administration of the investigational product.**

9.1.5.2 End of Study

The end of study 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.

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 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, the correlation between specific demographic data and PK, PD, and biomarkers may be explored.

9.2.1.3 Medical History

The Investigator or designee will collect a relevant medical, psychiatric, and surgical history that started within 5 years of enrollment or as necessary to describe 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. Findings are to be recorded 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 and severity will be collected for each condition that has not resolved.

9.2.1.4 Physical Examination

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

9.2.1.5 Concomitant Medications

All concomitant medications including over-the-counter products and vitamins administered while the subject is on study will be recorded on the eCRF.

9.2.1.6 Physical Measurements

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

9.2.1.7 Substance Abuse History

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

Note: Subjects who are taking methotrexate should be advised to limit alcohol consumption to no more than 4 ounces per week.

9.2.2 Efficacy Assessments

Efficacy assessments are recommended to be performed prior to obtaining any blood samples. Data will be captured on paper source. Data will be entered into the study database. **It is highly recommended that the same investigator performs efficacy assessments at every timepoint for a given subject.**

9.2.2.1 Hybrid Systemic Lupus Erythematosus Disease Activity Index

The hSLEDAI 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. Hybrid SLEDAI is the index score used during the validation of the SRI (Navarra et al, 2011; Furie et al, 2011). The hSLEDAI is identical to the SELENA-SLEDAI score except for the scoring of proteinuria, which uses the SLEDAI-2K definition (proteinuria is scored 4 points if proteinuria is > 0.5 grams/24 hours [or equivalent urine protein/creatinine ratio]). The hSLEDAI differs from SLEDAI-2K in 2 main aspects: the hSLEDAI includes scleritis and episcleritis for visual disturbances assessments and scores arthritis only if > 2 joints manifest signs of inflammation. In the hSLEDAI score, inflammation is strictly defined as the presence of tenderness plus one of the following: swelling, effusion, warmth or erythema. Unlike SLEDAI-2K, the presence of tenderness alone is not sufficient and at least 3 joints, and not only 2, must be affected. In this study, for hSLEDAI scoring purposes, arthritis is required to involve the small joints of hands and/or wrists. Additionally, in this study, scleritis and episcleritis will be considered for scoring purposes in the hSLEDAI only if SLE-relatedness is confirmed by an ophthalmologist.

A total hSLEDAI ≥ 6 is used for eligibility purposes, together with the presence of a clinical hSLEDAI ≥ 4. A clinical hSLEDAI score is a hSLEDAI score without the inclusion of points attributable to laboratory results.

Hybrid SLEDAI descriptors will be scored based on a review of medical history, physical examination, and clinical laboratory findings. Findings should reflect activity during the 30 calendar days prior to the current visit.

9.2.2.2 British Isles Lupus Assessment Group Index

The **British Isles Lupus Assessment Group (**BILAG**)** index (BILAG 2004) evaluates disease activity in 9 separate organ systems and comprises a total of 97 items. Each item is measured qualitatively by review of medical history and physical examination (yes/no, improving/same/worse/new) or quantitatively by measuring laboratory values. Based on these items, each of the 9 organ systems allocated an alphabetical score of A (most active), B (moderate activity), C (minor activity), D **(no activity)** or E (never present). BILAG descriptors will be scored based on a review of medical history, physical examination, and clinical laboratory findings. Findings should reflect activity during the 4-week period prior to the current visit and should be related to the subject's SLE.

9.2.2.3 Cutaneous Lupus Erythematosus Disease Area and Severity Index

The CLASI consists of 2 scores, the first summarizes the activity of the disease while the second is a measure of the damage done by the disease. Activity is scored based on erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss and non-scarring alopecia. Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia. Subjects are asked whether dyspigmentation due to cutaneous lupus lesion usually remains visible for more than 12 months, which is considered permanent. If so, the dyspigmentation score is doubled. The scores are calculated by simple addition based on the extent of the symptoms. The CLASI is designed as a table where the rows denote anatomical areas, while the columns score major clinical symptoms. The extent of involvement for each of the skin symptoms is documented according to specific anatomic areas that are scored according to the worst affected lesion within that area for each symptom.

9.2.2.4 Photography

In subjects who have a CLASI activity score ≥ 8 at screening, half body (from the neck down, anterior and posterior views) and cutaneous lupus lesion target area (global and close up excluding the face) photography will be taken and collected, if possible, per the photography manual. Photographs will be taken by the study staff at the time points specified in the Schedule of Activities (Section 2) and reviewed by vendor's team for quality and to ensure subject's de-identification before being reviewed by Amgen external adjudicator to ensure the visual characteristics of the rash are consistent with the CLASI score assigned.

9.2.2.5 Swollen and Tender Joint Count

Swollen and tender joint counts will be performed as noted in the Schedule of Activities (Section 2).

It **is** highly recommended that the same **investigator**/assessor should perform the assessments throughout the study for **a given** subject. The initials of the joint assessor should be recorded in the CRF. The score for each joint will be recorded on a paper source. Data will be entered into the study database.

Joints that have been replaced during the study, **or have suffered trauma or received intra-articular injections,** are considered non-evaluable. **Joints from subjects with osteoarthritis or other condition that in the investigator's opinion can cofound the assessment of lupus arthritis, are considered non-evaluable.**

Swollen Joint Count Assessments: A total 28 joints will be scored for presence or absence of swelling. A separated score for joints in the hands and wrists will be calculated.

Tender Joint Count Assessments: A total 28 joints will be scored for presence or absence of tenderness. A separated score for joints in the hands and wrists will be calculated.

Swollen and Tender Joint Count Assessments: joints in hands and wrists will be scored for the simultaneous presence or absence of swelling and tenderness.

9.2.2.6 Physician Global Assessment – Visual Analogue Scale

The **Physician Global Assessment (**PGA**)** is a visual analogue scale (VAS) using 3 benchmarks for assessing disease activity over the last 4 weeks. When scoring the PGA, the previous visit score should be noted, and the current score should be relative to that previous visit. The score ranges from 0 to 3 with 3 indicating severe disease. This refers to the most severe possible disease and does not reflect the most severe ever seen in a particular subject, but the most severe disease ever seen in all SLE patients. Therefore, a score of 3 should rarely be seen. Any disease rated greater than 2.5 is very severe. The range of moderate disease covers approximately 1.5 to 2.4. Mild disease falls below 1.5.

This is a global assessment, factoring in all aspects of the subject's lupus disease activity. It should not reflect non-lupus medical conditions. An increase of $\geq$ 0.3 points ($>$ 10% on the 3 point-VAS) from baseline is considered clinically significant worsening of disease. This assessment will be completed by a health care provider (HCP) and should be done before assessing the hSLEDAI and BILAG. The assessment will be

recorded on a paper source with both sources using the same dimensions and benchmarks for the VAS. Data will be transmitted or entered into the study database.

9.2.2.7 SELENA-SLEDAI Flare Index

The SELENA-SLEDAI Flare Index will be used to evaluate the presence of mild-moderate and severe flares as detailed in Buyon et al, 2005. An additional question will be added to the classic instrument if, based on the investigators' clinical judgment, the flare is mild or moderate.

9.2.2.8 BILAG Flare Index

The BILAG flare index will be derived from BILAG 2004, as measured by BILAG score designation of "worse" or "new" resulting in a B score in ≥ 2 organs or an A score in ≥ 1 organ (Gordon et al, 2003).

9.2.2.9 Lupus Low Disease Activity State (LLDAS)

The LLDAS will be calculated as detailed in Franklyn et al, 2016.

9.2.2.10 Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

The Systemic Lupus International Collaborating Clinic/American College of Rheumatology Damage Index global score will be calculated as detailed in Gladman et al, 1996.

9.2.2.11 Systemic Lupus Erythematosus Responder Index

The SRI-4 will be calculated as detailed in Luijten et al, 2012. **A subject achieves** SRI**-4 response if all of** the **following criteria are met:** ≥ 4**-**point reduction from baseline in hSLEDAI score, AND no new BILAG **2004** A score and no > 1 new BILAG B domain scores compared with baseline **(eg, no B, C, D, or E scores at baseline becomes A or no more than 1 C, D, or E score at baseline becomes B)**, AND no ≥ **0.3-**point **deterioration** from baseline in PGA VAS score (**scale 0 to 3**)**, AND no use of more than protocol-allowed therapies (ie, initiation or** increase **in OCS dose > 5 mg/day prednisone [or equivalent] or IM CS or IV CS at any time point during the study; initiation or increase in OCS dose ≤ 5 mg/day prednisone [or equivalent] after week 10; initiation or increase in OCS dose ≤ 5 mg/day prednisone [or equivalent] between week 0 and week 8 that was not returned to baseline dose within the following 2 weeks; increase in current or initiation of new immunosuppressant/immunomodulator(s) at any time during the study). The latest visit date among hSLEDAI, BILAG, and PGA will be considered the SRI-4**

visit date. In the case when all 3 visit dates are missing, the upper limit of the analytic window of this visit will be the SRI-4 visit date. When all **4** criteria are met, the subject is a responder at that time point according to the SRI-4 definition.

9.2.2.12 BICLA Index Response

The BICLA response is defined as at least 1 gradation of improvement in baseline BILAG domain scores in all body systems with moderate or severe disease activity at entry (eg, all A [severe disease] domain scores falling to B [moderate], C [mild], or D [no activity], and all B domain scores falling to C or D); no new BILAG 2004 A domain score and no > 1 new BILAG 2004 B domain scores compared with baseline; **no worsening of the hSLEDAI score from baseline; no** ≥ 0.3-point deterioration from baseline in PGA (scale 0 to 3); and no **use of more than protocol-allowed therapies (ie, initiation or increase in OCS dose > 5 mg/day prednisone [or equivalent] or IM CS or IV CS at any time point during the study; initiation or increase in OCS dose ≤ 5 mg/day prednisone [or equivalent] after week 10; initiation or increase in OCS dose ≤ 5 mg/day prednisone [or equivalent] between week 0 and week 8 that was not returned to baseline dose within the following 2 weeks; increase in current or initiation of new immunosuppressant/immunomodulator(s) at any time during the study);** and no initiation of non-protocol treatment **for SLE** (Wallace et al, 2011; Wallace et al, 2014).

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see Section 2. The investigator may utilize a qualified home health care service provider selected by Amgen at up to 8 home visits (including weeks 22, 26, 30, 34, 38, 42, 46, and 50), for subjects that have not experienced adverse events considered to be related to investigational product that in the opinion of the investigator may pose a risk for home health care administration of investigational product (home health care visits are not applicable for participating sites in Bulgaria). During those visits, in addition to administration of investigational product, safety assessments including vital signs, adverse events, serious adverse events, and concomitant medications review will be collected, as described in Section 7.8.2.

9.2.3.1 Adverse Events and Serious Adverse Events

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

9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) version 5 and is described in Section 12.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product (AMG 570/placebo) through the EOS are reported using the Event CRF.

9.2.3.1.1.2 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 the EOS are reported using the Event**s** CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 12.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

Since the criteria the CTCAE grading scale differs from the regulatory criteria for serious adverse events**, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life threatening status), it will be** left to the investigator's judgment to **also** report these abnormalities as serious adverse events**. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records**.

9.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period

After end of study, there is no requirement to **actively** monitor study subjects **after the study has ended with regards to study subjects treated by the investigator.** However, **if the investigator becomes aware of** serious adverse events **suspected to be related to the investigational product, then** these serious adverse events **will** be reported to Amgen within 24 hours following the investigator's **awareness** 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.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

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 Section 12.4.

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**s** CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If a 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 an investigational product 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 an investigational product 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 according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the IB and will notify the 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 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 Safety Monitoring Plan

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

9.2.3.1.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects will be collected after the start of investigational product through the EOS.

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 Section 12.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

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

Further details regarding pregnancy and lactation are provided in Section 12.5.

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 or seated position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. 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 should be oral or tympanic (with oral preferred). Once a location for temperature assessment is selected for a subject, the location should be the same throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.4 Clinical Laboratory Assessments

Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 2) 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 Section 12.2, 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.

[redacted]

9.2.4.2 Pregnancy Testing

A highly sensitive serum pregnancy test should be completed at screening and a highly sensitive urine pregnancy test should be completed at the Day 1 visit 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 Section 12.5). Refer to Section 12.5 for contraceptive requirements.

Additional pregnancy testing using a high sensitivity urine pregnancy test should be performed at monthly intervals during the treatment period and at the first 2 safety follow-up visits.

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

9.2.4.3 Tuberculosis Testing

All subjects must receive either a PPD, QuantiFERON®-TB, or T-spot test at screening.

9.2.4.3.1 Purified Protein Derivative

The PPD test must be read by a trained health care professional 48 to 72 hours after the test is placed. The PPD reader must be identified on the delegation of authority for this responsibility. PPD test kits will not be provided by the sponsor and must be procured locally.

9.2.4.3.2 QuantiFERON®-TB or T-spot Testing

If a QuantiFERON®-TB test is performed for eligibility, the test **can** be performed centrally with test kits provided**, or locally using a local kit procured by the site**. If a T-spot test is performed for eligibility, the test will be performed locally with test kits procured locally.

9.2.4.4 HIV Antibodies, Hepatitis B, and Hepatitis C Testing

Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C (HCAb), and HIV antibodies will be assessed at screening. If the results show a negative HBsAg and positive for HBcAb, quantification of hepatitis B virus DNA by PCR is necessary. Similarly, if the results show a positive HCAb, a quantification of hepatitis C virus RNA by PCR is necessary. The above mentioned PCR test results must be negative at screening for the subject to be eligible for this study.

9.2.5 Pharmacokinetic Assessments

All subjects randomized to treatment with AMG 570 will have PK samples assessed. Blood samples of approximately 4 mL will be collected for measurement of serum concentrations of AMG 570 as specified in the Schedule of Activities (Table 2-1 and Table 2-2). A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. 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 may unblind the study will not be reported to investigative study centers or blinded personnel until the study has been unblinded.

9.2.6 Pharmacodynamic Assessments

Blood samples for PD assessments will be collected as specified in the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.6.1 Biomarker Assessment During the Study

Blood samples will be collected for measurement of [redacted] at time points indicated in the Schedule of Activities (Table 2-1 and Table 2-2).

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 570. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

The final disposition of samples will be described in Section 12.6.

[redacted]

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.

The development of biomarkers can be useful 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 570.

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 Clinical Outcome Assessments: Patient Reported Outcomes

Patient reported outcomes should be completed by the patient alone before being clinically evaluated by the study nurse or physician.

The assessments will be recorded directly into the electronic tablet which will serve as the source documentation and will not be transposed to a CRF.

9.2.10.1 Medical Outcomes Short Form-36 Questionnaire Version 2

The SF-36v2 (acute version) Health Survey (Ware et al, 2000) contains 36 items and is a revised version of the SF-36 Health Survey. The SF-36v2 acute version is a patient-reported generic measure of health status. This survey yields assessments of 8 domains of health-related quality of life: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The scores from the 8 domains will be evaluated independently and aggregated into 2 norm-based summary component measures of physical and mental health. The recall period is the past 7 days.

This survey takes approximately 10 to 15 minutes to complete.

9.2.10.2 Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a Instrument (PROMIS Fatigue SF 7A)

The PROMIS Fatigue Short Form 7a is a 7-item instrument originally constructed by the PROMIS Fatigue team to represent the range of the fatigue trait (PROMIS Fatigue Scoring Manual). It assesses the experience of fatigue as well as its impact on physical,

mental, and social activities. Both psychometric properties and clinical input were used in the development of the short form from the PROMIS item bank. Estimates of responsiveness and minimally important differences have been reported for the 4 item PROMIS Fatigue instrument in SLE patients (Katz et al, 2019). The PROMIS Fatigue has also been able to differentiate disease activity in other rheumatologic diseases (Wohlfahrt et al, 2019).

The PROMIS Fatigue Short Form 7a takes 1 to 2 minutes to complete.

9.2.10.3 LupusQoL

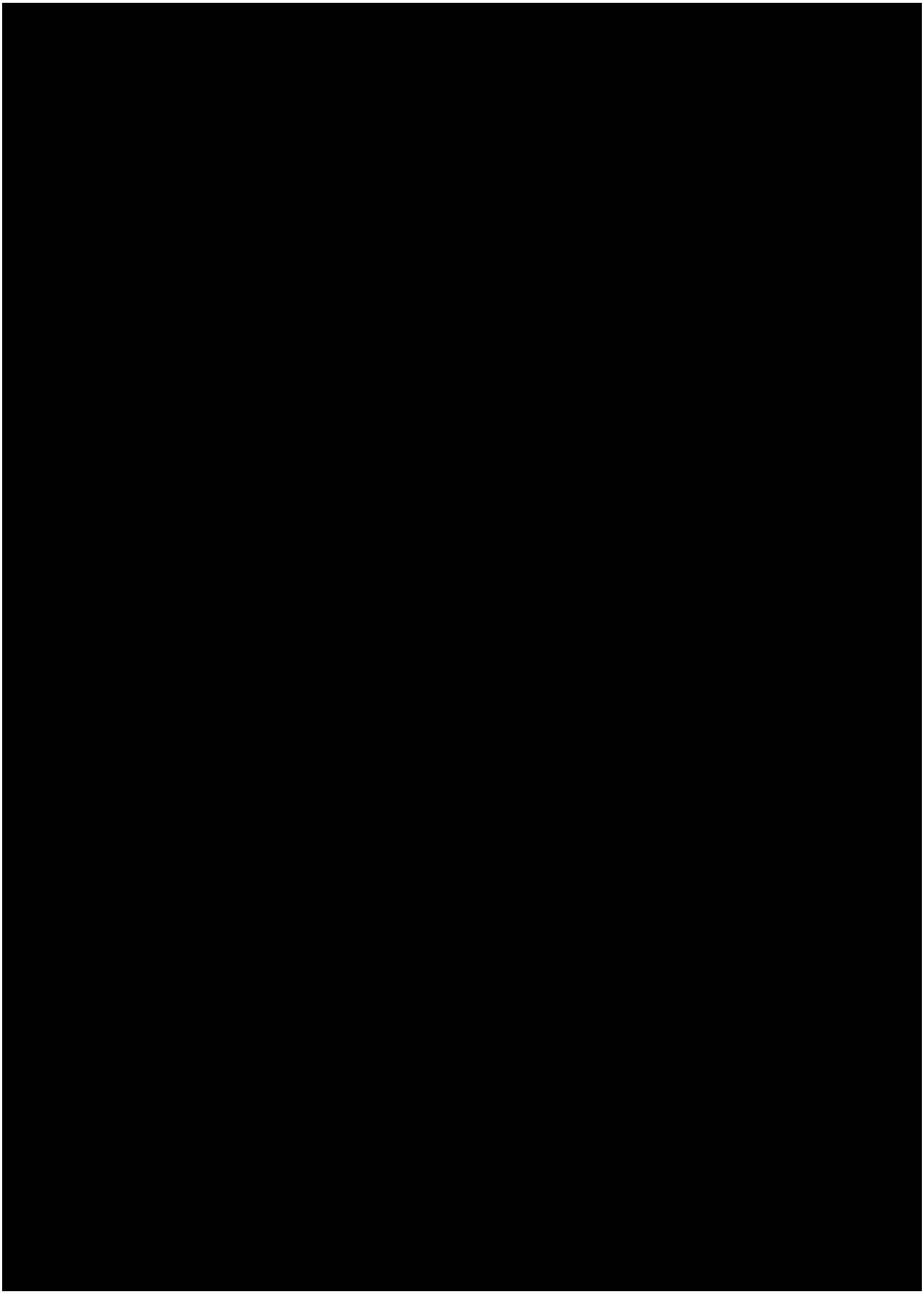
The **Lupus Quality of Life questionnaire (**LupusQoL**)** is a SLE-specific health-related quality of life instrument (Jolly et al, 2010; McElhone et al, 2007). The LupusQoL consists of 8 domains: physical health (8 items), pain (3 items), planning (3 items), intimate relationships (2 items), burden to others (3 items), emotional health (6 items), body image (5 items), and fatigue (4 items). The final instrument has demonstrated good internal reliability (Cronbach's 0.88 to 0.95), good test-retest reliability (r 0.72 to 0.93), good concurrent validity with the comparable domains of the SF-36 (r 0.71 to 0.79) and good discriminant validity for different levels of disease activity, measured by BILAG index, and damage (Systemic Lupus International Collaborating Clinics/ACR damage index) but not for all domains. The instrument also has acceptable ceiling effects and minimal floor effects.

Subjects typically complete the LupusQoL in less than 10 minutes. The scoring and the transformation of the scores takes approximately 5 minutes per subject.

9.2.10.4 Patient Global Assessment

The patient global assessment (PtGA) of disease activity typically assesses disease activity on a 10 cm **numerical rating** scale (**NRS**; 0 to 10 cm). The scale for the assessment ranges from “very well” (0) to “very poor” (10) (Furie et al, 2009). The validity of the PtGA in SLE has been established (Khraishi et al, 2014; Liang et al, 1989). The PtGA scale has a 7-day recall.

[redacted]



[redacted]

10. Statistical Considerations

10.1 Sample Size Determination

The approximate sample size of 320 subjects is chosen to provide 80% power to detect ≥ 25% absolute improvement for at least 1 AMG 570 dose group relative to placebo in the primary endpoint of SRI-4 response rate at week 52 at a significance level of 0.025 (1-sided) using a Bayesian Hierarchical Model, assuming a 40% response rate in placebo group.

Because enrollment can be stopped if early stopping rules for futility are met at an IA, the actual sample size could be smaller and cannot be pre-specified. The approximate sample size of 320 ensures if there is no interim signal for early termination based on futility of all AMG 570 doses, the trial will have adequate power to achieve the primary objective once all subjects have had the opportunity to complete week 52.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

10.2.1.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects randomized in the study, with treatment assignment based on subjects' randomized treatment assignment.

10.2.1.2 Safety Analysis Set

The Safety Analysis Set includes all randomized subjects who received at least 1 dose of investigational product and will be used to perform safety analyses according to the actual treatment received.

10.2.1.3 PK Concentration Analysis Set

The PK Analysis Concentration Set is defined as the subset of subjects in the Safety Analysis Set who had at least 1 evaluable serum concentration (including results below the level of detection) of investigational product. PK concentration data will be analyzed according to the actual treatment received.

10.2.1.4 PK Parameter Analysis Set

The PK parameter analysis set is defined as the subset of subjects in the Safety Analysis Set who had at least one PK parameter adequately derived. PK parameter will be analyzed according to the actual treatment received.

10.2.1.5 PD Analysis Set

The PD analysis set is defined as the subset of subjects in the Safety Analysis Set who had at least one evaluable PD parameter measurement collected. PD parameter will be analyzed according to the actual treatment received.

[redacted]

10.2.2 Covariates

The baseline covariates may include but are not limited to:

- Age, region, race, **sex**
- Baseline SLE disease activity
- Baseline background medications (detectable vs undetectable baseline SLE SOC drug levels)

[redacted]

Other covariates may be evaluated as necessary. Stratification factors will be included as covariates in the model or be used to examine treatment effect in subgroups. If included as covariates in the model for treatment comparisons, the IRT value will be used to be consistent with the randomization scheme. The impact of the baseline covariates on the treatment effect may be explored and adjusted in the model for the primary and secondary endpoints as deemed necessary.

10.2.3 Subgroups

In addition to stratification factors, some covariates mentioned above may be used for further exploration in subgroups. For subgroup analysis, the value collected from source-verified eCRF will be used to reflect the true clinical relevance of the covariate.

10.3 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before any database lock. To preserve study integrity, the primary analysis will be conducted after all

subjects have had the opportunity to complete week 52 and the final analysis will be conducted and reported following the EOS, as defined in Section 5.3.1.

10.3.1 Planned Analyses

10.3.1.1 Interim Analysis and Early Stopping Guidelines

Interim analyses will be conducted to allow adaptation of the randomization ratio to the 3 AMG 570 treatment groups, holding the allocation to placebo constant at 25%, and assessing efficacy for early futility or administrative success decisions:

- The study team, investigators, and subjects will remain blinded to the investigational product, changes in randomization allocation probabilities, and results of the interim analyses.
- The first IA will be executed after the first enrolled 40 subjects are randomized and have had the opportunity to complete the week 24 assessment. Subsequent IAs are scheduled after every additional 32 subjects are randomized and have had the opportunity to complete the week 24 assessment until full enrollment. The last IA will occur when all 320 subjects are randomized and have had the opportunity to complete the week 24 assessment. This IA will be referred to as the 'all-subjects-week-24' IA.
- Efficacy analyses will be performed at IAs to assess the likelihood of AMG 570 being superior to placebo by a clinically meaningful difference.
  - If this likelihood is unacceptably low for all dose levels, the trial is recommended to stop for futility.
- Additionally, at the 'all-subjects-week-24 IA', if this likelihood is sufficiently high at, at least 1 dose level, IA triggers an administrative success signal. This would not alter ongoing or planned activities of this phase 2b study, but downstream activities may be planned/initiated (eg, a phase 3 study). Analysis planned at each IA are listed in Table 1-1.

At IAs,

- Beginning with the second IA and before the last IA, enrollment to the study may be stopped for futility if the posterior probability of achieving a clinically meaningful difference in SRI-4 response rates of at least 15% between each active treatment group and placebo is below 2.5%.
- Once all subjects have had the opportunity to complete the week 24 visit, the primary efficacy analysis model, a Bayesian Hierarchical Model will be fitted to the week 52 SRI-4 response data with longitudinal modeling of earlier visits week 16, 20, and 24 to compute the predictive probability of success in a hypothetical, future phase 3 study If the predictive probability of success in this hypothetical future phase 3 study is larger than 80% for any of the AMG 570 dose groups, downstream activities may be planned/initiated. Regardless of the result of this IA, the conduct of the current study will not be impacted; the current study will continue until all subjects have had the opportunity to complete the week 52 visit and safety follow-up.

10.3.1.2 Primary Analysis

The primary analysis will take place when all subjects have had the opportunity to complete week 52.

At primary analysis:

- The efficacy goal of the study is to demonstrate the superiority of AMG 570 relative to placebo.
- The primary analysis of the primary endpoint SRI-4 at week 52 is a Bayesian Hierarchical Model which borrows information dynamically across the 3 active AMG 570 treatment groups while controlling the overall type I error at the 1-sided 2.5% level.
- The null hypothesis will be rejected (ie, study will be claimed successful) if the posterior probability of superiority of any active AMG 570 treatment group is above 0.981. This threshold was chosen to preserve a simulated overall 1-sided type I error rate to be less than 2.5%.

10.3.1.3 Final Analysis

The final analysis will be completed after study completion is reached, after the last subject reaches the last visit during the safety follow-up period, and all data are collected for the study.

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

All categorical variables will be summarized using the number and percent of subjects falling into each category and all continuous variable will be summarized using mean, standard error or standard deviation, median, Q1, Q3, minimum, maximum, and number of subjects with observations. Subgroup analyses (by certain demographic variables and stratification factors as appropriate) will be presented if deemed necessary. Safety endpoints will be summarized descriptively.

10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods to Support Estimands
Primary	Bayesian Hierarchical Model will be used to evaluate primary efficacy estimand.
Secondary	Bayesian Hierarchical Model/Generalized linear model will be used to evaluate secondary efficacy endpoints. Details will be described in the SAP.
Exploratory	Details of the analysis of exploratory endpoints will be specified in the SAP.

10.3.2.3 Safety Analyses

10.3.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary*	All safety analyses will be performed using the Safety Analysis Set based on subject's actual treatment received. Safety analysis will include analyses of AEs, clinical laboratory tests, vital signs, and [redacted]

*Safety endpoints are not primary endpoints for this study

10.3.2.3.2 Adverse 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, and adverse events leading to withdrawal from investigational product or other protocol-required therapies will also be provided.

10.3.2.3.3 Laboratory Test Results

Clinical laboratory test results and change from baseline will be summarized over time by each treatment group. In addition, shift tables, from baseline to the worst on-study laboratory toxicity based on the latest version of CTCAE grading, will be presented.

10.3.2.3.4 Vital Signs

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by each treatment group.

10.3.2.3.5 Physical Measurements

Clinically significant findings from physical examinations will be listed by subject and assessed for clinical significance which will be included in the adverse event listings and summaries.

[redacted]

10.3.2.3.7 Exposure to Investigational Product

Summary statistics will be provided for the total number of doses administered, total dose received, and total duration of investigational product exposure by treatment.

10.3.2.3.8 Exposure to Other Protocol-required Therapy

Descriptive statistics of total dose (mg), dosage categories, duration of usage, number and percentage of subjects with dose modifications, and reasons for modification will be produced to describe the exposure by treatment group from baseline to end of study.

10.3.2.3.9 Exposure to Concomitant Medication

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

10.3.2.4 Other Analyses

Serum concentrations will be summarized descriptively by treatment for each PK sampling time point using PK Concentration Analysis Set. PK parameter (if deemed necessary) will be summarized with PK parameter analysis set. PD parameter (if deemed necessary) will be summarized with PD analysis set. Medical history will be summarized by SOC and PT and tabulated by treatment group and total using the Safety Analysis Set according to the actual treatment received.

11. References

AMG 570 Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

Adams A, MacDermott EJ, Lehman TJ. Pharmacotherapy of lupus nephritis in children: a recommended treatment approach. Drugs. 2006;66:1191-1207.

Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis & Rheum 2019*; 71(9):1400-1412

Arthritis & Rheumatism (Arthritis Care & Research), Vol. 61, No. 9, September 15, 2009, pp 1168-1178.

Buyon JP, Petri MA, Kim MY, et. al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: A randomized trial. *Ann Intern Med*. 2005;142:953.

Chandran V, Bhella S, Schentag C, Gladman DD. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. *Ann Rheum Dis*. 2007;66: 936-939.

Cheng LE, Amoura Z,Cheah B, et al. Brief Report: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multiple-Dose Study to Evaluate AMG 557 in Patients With Systemic Lupus Erythematosus and Active Lupus Arthritis. Arthritis Rheumatol. 2018 Jul;70(7):1071-1076.

Doria A, Stohl W, Schwarting A, et al. Efficacy and Safety of Subcutaneous Belimumab in Anti-Double-Stranded DNA-Positive, Hypocomplementemic Patients With Systemic Lupus Erythematosus. Arthritis Rheumatol. 2018 Aug;70(8):1256-1264.

Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis. 2016 Sep;75(9):1615-1621.

Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011 Dec;63(12):3918-30.

Furie RA, Petri MA, Wallace DJ, et al. Novel evidence-based systemic lupus erythematosus responder index. Arthritis & Rheum. 2009;61(9):1143-1151.

Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the systemic lupus international collaborating clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus. *Arthritis Rheum.* 1996;39(3):363-369.

Gordon C, Sutcliffe N, Skan J, et al. Definition and treatment of lupus flares measured by the BILAG index. Rheumatology. 2003;42(11):1372-1379.

Jolly M, Pickard AS, Wilke C et al. Lupus-specific health outcome measure for US patients: the LupusQoL-US version. Ann Rheum Dis. 2010;69:29-33.

Katz P, Pedro S, Alemao E, et al. Estimates of responsiveness, minimally import differences and patient acceptable symptom state in five patient-reported outcomes measurement information system short forms in systemic lupus erythematosus. ACR Open. 2019: 1-8. Doi 10.1002/acr2.11100.

Khraishi M, Aslanov R, Dixit S, et al 2014. The validity of patient and physician global disease activity assessments of systemic lupus erythematosus: results from the lupus activity coring tool (LAST) as compared to the Selena Sledai (SS) modification multicentre study. ACR 2014.

Kotzin BL. Systemic lupus erythematosus. Cell. 1996;85:303-306.

Liang MH, Socher SA, Larson MG, Schur PH. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum. 1989;32(9):1107-18.

Luijten KMAC, Tekstra J, Bijlsma JWJ, Bijl M. The Systemic Lupus Erythematosus Responder Index (SRI): A new SLE disease activity assessment. *Autoimmun Rev.* 2012;11(5):326-329.

McElhone K, Abbott J, Shelmerdine J et al. Development and validation of a disease-specific health-related quality of life measure, the LupusQol, for adults with systemic lupus erythematosus. Arthritis Rheum. 2007;57:972-979.

Miyakis S, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Journal of Thrombosis and Haemostasis, 2006; 4: 295–306.

Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011 Feb 26;377(9767):721-731.

Pisetsky DS, Clowse MEB, Criscione-Schreiber LG, et al. A Novel System to Categorize the Symptoms of Systemic Lupus Erythematosus. Arth Care Res. 2019; 71 (6): 735-741.

PROMIS Fatigue Scoring Manual. Accessed at http://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Fatigue_Scoring_Manual.pdf on 29 Jan 2020

Rhaman A and Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358: 929-939.

Sullivan BA, Tsuji W, Kivitz A, et al. Inducible T-cell co-stimulator ligand (ICOSL) blockade leads to selective inhibition of anti-KLH IgG responses in subjects with systemic lupus erythematosus. Lupus Science & Medicine 2016;3: e000146.

Wallace, D, Kalunian K, Petri, M, et al. Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. Ann Rheum Dis. 2014;73:183-190.

Wallace D, Strand V, Furie R, et al. Evaluation of Treatment Success in Systemic Lupus Erythematosus Clinical Trials; Development of the British Isles Lupus Assessment Group-Based Composite Lupus Assessment Endpoint. Arth Rheum. 2011;63-s894 ACR.

Ware JE. SF-36 Health Survey Update. SPINE. 2000; 25:3130-3139.

Wohlfahrt A, Bingham CO, Marder W, et al. Responsiveness of patient-reported outcomes measurement information system measures in rheumatoid arthritis patients starting or switching a disease-modifying antirheumatic drug. Arth Car Res 2019: (4): 521-529.

Zhang F, Bae SC, Bass D, et al. A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. Ann Rheum Dis. 2018 Mar;77(3):355-363.

12. Appendices

12.1 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
[redacted]	
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BAFF	B cell activating factor
BICLA	BILAG based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
CFR	Code of Federal Regulations
CLASI	Cutaneous Lupus Erythematosus Area and Severity Index
Clinical hSLEDAI	**hybrid** SLEDAI assessment score without the inclusion of points attributable to any laboratory **parameter,** including urine **and** immunologic **parameters**.
C_{max}	maximum observed concentration
CNS	central nervous system
CPK	creatine phosphokinase
CS	**corticosteroids**
CTCAE	common terminology criteria for adverse events
DILI	**drug-induced liver injury**
DMC	data monitoring committee
eCRF	electronic case report form
EDC	electronic data capture
End of Study for individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
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
EOS	end of study
Exposure-response analysis	mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic [PK] exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic (PD) effects, efficacy and safety endpoints.
FAS	Full Analysis Set
FIH	first in human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HBcAb	hepatitis B core antibody
HCP	health care provider
HBsAg	hepatitis B surface antigen

Abbreviation or Term	Definition/Explanation
HepCAb	hepatitis C antibody
HIV	Human Immunodeficiency Virus
HRT	hormonal replacement therapy
hSLEDAI	Hybrid Systemic Lupus Erythematosus Disease Activity Index
IA	interim analysis
IB	Investigator's Brochure
IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Council for Harmonisation
ICOS	inducible co-stimulator
ICOSL	inducible co-stimulator ligand
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL-2	Interleukin 2
IM	**intramuscular**
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Boards
IRT	interactive response technology
IV	intravenous
JAK	**janus kinase**
KLH	Keyhole limpet hemocyanin
LDH	lactate dehydrogenase
LLDAS	Lupus Low Disease Activity State
LupusQoL	**Lupus Quality of Life questionnaire**
MCTD	mixed connective tissue disease
MDRD	Modification of Diet in Renal Disease
[redacted]	
NOAEL	no-observed-adverse-effect-level
NSAID	Non-steroidal Anti-inflammatory Drugs
OCS	oral corticosteroids
PCR	polymerase chain reaction
PD	pharmacodynamic
PtGA	**Patient Global Assessment**
PGA	Physician Global Assessment
[redacted]	
PI	Principal Investigator
PK	pharmacokinetic
PPD	purified protein derivative
PROMIS	Patient-Reported Outcome Measurement Information System
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks

Abbreviation or Term	Definition/Explanation
QW	once-weekly
RA	rheumatoid arthritis
RAR	Response Adaptive Randomization
RBC	red blood cell
RO	receptor occupancy
ROW	rest of the world
SAP	Statistical Analysis Plan
SC	subcutaneous
SDI	Systemic Lupus International Collaborating Clinic / American College of Rheumatology Damage Index
SF-36v2	Medical Outcomes Short Form 36 version 2 questionnaire
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SOA	schedule of assessments
SOC	standard of care
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	Systemic Lupus Erythematosus Responder Index
study day 1	defined as the first day that protocol-specified investigational product is administered to the subject
TBL	total bilirubin
ULN	upper limit of normal
VAS	visual analogue scale

12.2 Appendix 2. Clinical Laboratory Tests

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[a]

Central Laboratory: Chemistry	Central Laboratory: Coagulation	Central Laboratory: Urinalysis	Central Laboratory: Hematology	Central Laboratory: Other Labs
Sodium	PT/INR	Protein/creatinine ratio	Central Laboratory:	Central Laboratory:
Potassium	aPTT	Specific gravity	RBC	Hep B surface antigen
Chloride	Fibrinogen[b]	pH	Nucleated RBC	Hep B core antibody
Bicarbonate	D-dimer[b]	Blood	Hemoglobin	Hep B virus DNA[c]
Total protein		Protein	Hematocrit	Hep C antibody
Albumin		Glucose	MCV	Hep C virus RNA[d]
Calcium		Bilirubin	MCH	Antinuclear antibody
Adjusted calcium		WBC	MCHC	[redacted]
Magnesium		RBC	RDW	HIV antibody
Phosphorus		Epithelial cells	Reticulocytes	[redacted]
Glucose		Bacteria	Platelets	Serum pregnancy test
BUN or Urea		Casts	WBC	[redacted]
Creatinine		Crystals	Differential	QuantiFERON®-TB[f]
Uric acid			• Bands/stabs	Local Laboratory:
Total bilirubin			• Eosinophils	Urine Pregnancy
Direct bilirubin			• Basophils	T-spot[f]
ALP			• Lymphocytes	FSH[g]
LDH			• Monocytes	Coombs test[h]
AST (SGOT)			• Total neutrophils	
ALT (SGPT)			• Segmented neutrophils	
Creatinine clearance by MDRD			Local Laboratory:	
GGT			Erythrocyte sedimentation rate	
C-reactive protein				
Total Cholesterol				
HDL				
LDL				
Triglycerides				
Creatinine Phosphokinase				

Footnotes defined on next page

[redacted] ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted] aP**T**T = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle stimulating hormone; GGT = gamma glutamyl transpeptidase; HDL = high density lipoprotein; Hep = hepatitis; HIV = Human Immunodeficiency Virus; [redacted] INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density liproprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MDRD = Modification of Diet in Renal Disease; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count

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.

[a] **Approval for applicable local lab testing may be granted by sponsor as needed in the event that central lab testing is unavailable.**

[b] In case of drug-induced liver injury (DILI) events.

[c] In case of Hep B surface antigen negative and Hep B core antibody positive.

[d] In case of Hep C antibody positive.

[e] Lupus reflex will be done if aPTT is prolonged.

[f] For tuberculosis testing at screening, QuantiFERON®-TB OR T-spot test OR **purified protein derivative (**PPD**) test** can be used. **QuantiFERON®-TB can also be done locally.**

[g] In case the investigator needs to confirm postmenopausal status (and patient is not taking hormone replacement therapy).

[h] For suspicion of hemolytic anemia (per the investigator's judgment).

12.3 Appendix 3. Study Governance Considerations

Independent Data Monitoring Committee

An Independent Biostatistics Group (IBG) will perform the interim analysis and provide the interim report to an independent unblinded Data Monitoring Committee (DMC). The DMC will review all available safety and efficacy data periodically (Table 1-1). The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and Data Monitoring Group will not have any direct contact with study site personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master folder (TMF) at the conclusion of the study. Further details are provided in the DMC charter.

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

The protocol, protocol amendments, informed consent form, IB, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (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

Recruitment Procedures

Site staff will identify potential subjects from their existing patient population or may seek referral patients through existing professional networks or other community sources such as patient advocacy groups. All patient facing materials must be reviewed/approved by the sponsor (Amgen Inc.) and the local IRB/IEC.

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

Subjects must be informed that their participation is voluntary. Subjects or his/her legally authorized representative 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 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 or his/her legally authorized representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from investigational product 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 or the subject's legally authorized representative.

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 33 days from the previous informed consent form signature date.

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future 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 future 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 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, multi-center 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 multi-center 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 and 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.

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 Interactive Response Technology (IRT) system (if used, such as subject ID 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.

To include the following:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, IB, 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

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.

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

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 investigational product. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the SAP.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after investigational product 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 investigational product 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 and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF). • The investigator must assign the following adverse event attributes: o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); o Dates of onset and resolution (if resolved); o **Did the event start prior to first dose of investigational product** o **Assessment of seriousness;** o Severity (or toxicity defined below); o Assessment of relatedness to investigational product (AMG 570/placebo), protocol-required therapies and/or study-mandated activity/study procedure; o 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**s** CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the Event**s** 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, version 5 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 (AMG 570/placebo), study-mandated activity/study procedure and/or other protocol-required therapies 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 investigational product 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**s** 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. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using the electronic Serious Adverse Contingency Report Form (this is a paper-based 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 the paper-based Serious Adverse Event Contingency Report Form (**see Figure 12-1**). • **Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.**

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

A **Study # 20170588** **AMG 570**	**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

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

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?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? AMG 570 No ✓ Yes ✓	**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 570	☐ Blinded ☐ Open Label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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A **Study # 20170588** **AMG 570**	**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		Continuing		Dose	Route	Freq.	Treatment Med	
			No✓	Yes✓	No✓	Yes✓				No✓	Yes✓

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

A Study # 20170588 AMG 570	**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	Title	Date
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.		

12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

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

Contraceptive use and methods should be consistent with local regulations for subjects participating in clinical studies.

Female subjects of childbearing potential should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant during treatment and for a period of at least 10 weeks after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternative medical cause (eg. Mullerian agenesis, androgen insensitivity, and gonadal dysgenesis), can be considered not of childbearing potential.

Note: bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A woman age < 55 years with no menses for at least 12 months and with a follicle stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

- 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 investigational products; 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)

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 the final safety assessment.
- Information will be recorded on the Pregnancy Notification Form (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 Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through at least 10 additional weeks 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.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the investigational product by the investigator, will be reported to Amgen Global Patient Safety as described in Section 12.4. 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 at least 10 additional weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (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 Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through at least 10 additional weeks after the last dose of investigational product (Section 9.1.5).
- Information will be recorded on the Lactation Notification Form (Figure 12-3) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Investigational product will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 223.
- 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 the final safety assessment after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy Notification Form

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: _20170588_____

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 12-3. Lactation Notification Form

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: 20170588

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

12.6 Appendix 6. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Activities (Section 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 570 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 Section 12.3 for subject confidentiality.

12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Investigational Product 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 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, rhabdomyolysis, 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	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values
	> 5x ULN but < 8x ULN for ≥ 2 weeks	
	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule	> 3x ULN (when baseline was < ULN)
	> 3x 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	> 8x 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 Amgen 570 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 Section 12.4.

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. **Tests may be performed locally as required per investigator discretion.**

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL > 2x 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 (Ig)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, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or 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.

Amendment 3

Protocol Title: A Phase 2b Dose Ranging Study to Evaluate the Efficacy and Safety of Rozibafusp Alfa (AMG 570) in Subjects With Active Systemic Lupus Erythematosus (SLE) With Inadequate Response to Standard of Care (SOC) Therapy

Amgen Protocol Number AMG 570 20170588

EudraCT Number 2019-000328-16

NCT Number 04058028

Amendment Date: 24 May 2022

Rationale:

This protocol amendment removes the requirement for an independent blind joint assessor to conduct joint count assessments (number of tender and swollen joints). There is no need to have a separate blinded assessor to perform joint count, since for the primary endpoint and other main efficacy endpoints this assessment is performed by the investigator from each site, who have the required training and are performing all efficacy assessments. Additional minor updates were incorporated into this amendment which in general represent clarifications and grammatical corrections. The following changes were included:

1. Efficacy Assessments:
    - Remove requirement for a separate blinded joint assessor (section 9.2.2.5).
    - Clarify that the same investigator must perform all efficacy assessments at every time point for a given subject. In order to ensure consistency, it is clarified that the same investigator/assessor should perform the assessments throughout the study for a given subject (sections 9.2.2 and 9.2.2.5).
    - Clarify data collection process (sections 9.2.2, 9.2.2.5, and 9.2.2.6).

- Improve clarity of the definition of Systemic Lupus Erythematosus Responder Index (SRI-4) response in section 9.2.2.11 and British Isles Lupus Assessment Group (BILAG)-based Combined Lupus Assessment (BICLA) response in section 9.2.2.12.
- Clarify events that classify joints as non-evaluable (section 9.2.2.5).

2. Updates to Primary Estimand include (sections 1.1 and 4.1):
   - Clarify that SRI-4 response cannot be achieved regardless of protocol deviations, since the Important Protocol Deviation list is now used to define 'more than protocol-allowed therapies'.
   - Remove language defining SRI-4 response from the Objectives/Endpoints table, as it is described in detail in other sections of the protocol.
3. Clarifications to Objectives and Endpoints include (sections 1 and 4.1):
   - Endpoint for secondary objective aiming to evaluate efficacy of AMG 570 on joint count was updated to clarify that the combined tenderness and swelling of joint count will be conducted for joints in hands and wrists, as it is described in section 9.2.2.5.
   - Clarify that the endpoint for secondary objective aiming to describe efficacy of AMG 570 using patient-reported outcomes includes the 2 component measures of physical and mental health to be assessed by the Medical Outcomes Short Form 36 version 2 Questionnaire, as it is described in section 9.2.10.1.

4. Clarifications were provided on study duration and safety follow-up for subjects that complete the 52-week treatment period and for subjects who discontinue the

investigational product earlier. These clarifications were incorporated to multiple sections of the protocol (sections 5.1, 5.3.2, 9.1.3, 9.1.5.1, and Table 2-2).

- Timing of sample collection for pharmacokinetic (PK) and [redacted] assessments during safety follow-up was described for clarity purposes (section 9.1.3).
- Additionally, for simplification and improved clarity, information pertaining to safety follow-up was removed from protocol synopsis, overall design description, and treatment period (sections 1.1, 5.1, and 9.1.2)

5. Clarification of when an individual subject is considered to have completed the study (sections 5.3.2 and 9.1.5.1).
6. Clarify within the table for Analyses Schedule that after the 7th interim analysis, additional interim analyses are planned after every 32 subjects are randomized and have had the opportunity to complete the week 24 assessment until full enrollment (Table 1-1).
7. Interim analysis language was updated to remove details related to the hypothetical Phase 3 study as they do not impact the conduct of this study and will be pre-specified in the study data monitoring committee charter, statistical analysis plan, and simulation report, as appropriate (section 10.3.1).
8. Clarify that the adjudication reviews occur at study entry to determine eligibility and throughout the study period on blinded endpoint data from enrollment to week 52 for all randomized subjects and for all visits (section 5.1).
9. Clarify that subjects taking more that protocol-allowed therapies are considered treatment failures for the primary efficacy endpoint analyses but will be allowed to continue investigational product and/or the study at the investigator's discretion except those initiating specific treatments with immunosuppressant/immunomodulators (sections 5.1, 7.1.4.1, and 7.1.7).
    - Section 7.1.7 is listing all the treatments preventing a subject from continuing treatment with investigational product.

10. Title of section 9.2.6.1 was changed to Biomarker Assessment During the Study given that not all biomarkers listed in that section have established pharmacodynamic activity.

11. Specify that all subjects who at the end of study visit have clinical sequelae considered potentially related to an [redacted] response will be asked to return for additional testing. Additionally, it was clarified that follow-up results will be communicated to sites after database is locked to prevent potential risk of unblinding the sites for treatment assignment (section 9.2.8).

12. Clarify what is included in baseline covariates (section 10.2.2).

13. Inclusion criteria:

    - Clarify inclusion criterion 105 by re-organizing Systemic Lupus Erythematosus (SLE) treatments that subjects must be taking to meet protocol-specific rules applied during screening. One treatment was included to this criterion, leflunomide (update also incorporated in section 7.4.2.2).

14. Exclusion criteria:

    Other Medical Conditions

    - For consistency, criterion 208 was updated to align with the updates made to Schedule of Activities regarding monitoring of viral load frequency to evaluate hepatitis B and C.

    Prior/Concomitant Therapy was updated to:

    - Add thalidomide treatment within 4 weeks prior to screening to the treatment listed in exclusion criterion 212. For consistency, thalidomide was also added as an excluded treatment during study period (section 7.1.7).
    - Decreased washout period for Janus kinase (JAK) inhibitor from 3 to 1 month prior to screening based on information available for the pharmacokinetic/pharmacodynamic profile of these drugs (criterion 213).
    - Clarify criterion 215 by adding immunosuppressive or immunomodulatory activity to treatment with a biologic agent, reduce washout period for abatacept to

3 months prior to screening based on its pharmacokinetic/pharmacodynamic profile, and clarify that pharmacodynamic activity of other biologics at screening should be considered when evaluating washout periods.

- Clarify the timeframe within which a subject must not plan to receive a live vaccine (criterion 217).

Prior/Concurrent Clinical Study Experience:

- Revise washout period for treatment with an investigational product or device to consider the pharmacokinetic and pharmacodynamic profile of those products at screening (criterion 219).

Diagnostic Assessments:

- Include Gilbert's Syndrome as an exception for presence of laboratory abnormalities during screening in serum total bilirubin since these patients present non clinically relevant elevated bilirubin levels (criterion 221).

Other Exclusions was updated to:

- Clarify that serum pregnancy test is required at screening and urine pregnancy test is required at day 1 visit (criterion 225).

15. Schedule of Activities-Safety Follow-up Period was updated to (Table 2-2):
    - Clarify that this table applies for the subset of subjects that completed the planned 52-week treatment period and emphasize that subjects are required to attend as many visits as necessary to ensure a minimum of 16 weeks of safety follow-up after last dose of the investigational product.
    - Clarify that safety follow-up visits should be scheduled in relation to last administration of the investigational product and not visit week 52.
    - Add frequency for monitoring viral load to evaluate hepatitis B and C.
    - Remove urine pregnancy tests from the last two safety follow-up visits.

16. Minor updates were included in the footnotes of the Schedule of Activities Treatment Period to clarify information regarding starting time of home health care visits, the option of conducting a QuantiFERON-TB test locally, assessment frequency of serum viral DNA and RNA for hepatitis B and C, and [redacted]. Additionally, for clarity purposes details no longer relevant to the assessments were removed (Table 2-1 footnotes e, f, g, i, q, and r).

17. Accountability instructions for AMG 570 was updated to remove requirement to record the amount used in AMG 570 preparation on the electronic case report form for each subject (Table 7-1).

18. Simplify language around disease flares as a possible reason to discontinue protocol-required investigational product or procedural assessments (section 8.1).

19. The description of AMG 570 was updated (section 3.2.2).

20. For rescreening, it was clarified that tuberculosis tests and serologies for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus (HIV) are not required to be repeated when rescreening occurs within 12 months of screening visit, provided that those test results were negative and there is no patient's medical/epidemiological history suggestive of infection or recent exposure to cases of infection (section 9.1.1).

21. Clarify the types of corticosteroid treatments that are allowed in the study and specify that subjects requiring such treatments can continue the investigational product at the investigator's discretion (section 7.1.4.2).

22. Simplify Treatment Period section by removing information outside the scope of this section (section 9.1.2).

23. Include the option for local laboratory to conduct the QuantiFERON-TB test for eligibility using a local kit procured by the site (section 9.2.4.3.2).

24. Clarify the rating scale used for patient global assessment of disease activity (section 9.2.10.4).

25. Information collected for screen failure was updated to remove medical history and prior therapies as these are not considered required forms for screen failure per electronic case report form standard instructions (section 6.5).

26. Remove the efficacy analysis set (section 10.2.1.2).

27. Include a footnote in Analyte Listing table to instruct that local lab testing may be conducted if central lab testing is unavailable and add that QuantiFERON-TB test can also be conducted locally. For clarity purposes, details no longer relevant to the analyte listing were removed (Table 12-1 footnotes a, b, and f).

28. Add a clarification note that clinical assessments to evaluate hepatoxicity in subjects for whom investigational product is withheld due to potential drug-induced liver injury can be performed locally as required per investigator discretion (section 12.7).

29. Updates have been implemented to align collection and reporting of safety events with current procedures (Table 2-1, Table 2-2, sections 7.1.6, 9.2.3.1.1.2, 9.2.3.1.1.3, and 12.4).

30. Clarify that tapering of oral corticosteroids is allowed before week 24 at the investigator's discretion (sections 1.1 and 7.1.4.2).

[redacted]

32. The definition of the alphabetical score used to evaluate disease activity in 9 separate organ system was updated only for D by replacing stable with no activity (section 9.2.2.2).

33. Administrative, typographical, abbreviations, and formatting changes were made throughout the protocol.

Superseding Amendment 2

Protocol Title: A Phase 2b Dose Ranging Study to Evaluate the Efficacy and Safety of Rozibafusp Alfa (AMG 570) in Subjects with Active Systemic Lupus Erythematosus (SLE) with Inadequate Response to Standard of Care (SOC) Therapy

Amgen Protocol Number AMG 570 20170588

Amendment Date:	13 October 2020
Superseding Amendment Date:	11 November 2020

Superseding Amendment 2 Summary of Changes:

- Incorporate changes to align with the Data Monitoring Committee (DMC) Charter:
  - Change 'Futility' to 'Administrative Success' in Table 1-1.
  - Revise administrative success cutoff value from 85 to 80%.
  - Remove 'moderate to severe' from BILAG flare endpoint.
  - Relocate the SLEDAI-2K proteinuria definition for clarity.
  - Clarify efficacy assessment data will be captured either on an electronic or paper source and transmitted or entered into the study database.
- Clarify SLE-related eligibility will be reviewed and confirmed by the adjudication team.
- Delete Appendix 8. Data Collection to align with the updated Amgen protocol template.

Amendment 2 Summary of Changes:

- Incorporate changes to the study design to enable the study to support registration, if the results are positive; these changes include:
  - Update study from phase 2 to phase 2b.
  - Revise primary endpoint to SRI-4 response rate at week 52 and make SRI-4 response rate at week 24 a secondary endpoint.
  - Change all key secondary endpoints to secondary endpoints and add secondary disease flare endpoints.
  - [redacted]
  - Revise statistical methods, including sample size estimate, planned analyses, and efficacy analyses methods for primary and secondary endpoints.

- Clarify options for a subject to proceed in the study if the subject discontinues investigational product prior to week 52.
- Clarify contraceptive guidance and pregnancy and lactation information:
  - Adjust the duration for contraceptive requirements and collection of pregnancy and lactation information to at least 10 additional weeks after the last dose of investigational product for female subjects of childbearing potential.
  - Specify that pregnancy testing should be performed monthly during both the treatment period and at the first 2 safety follow-up visits.
  - Clarify the definition of females of childbearing potential.
- Specify home health care visits will be centrally provided by the sponsor starting at week 22 and will be optional for subjects who have not experienced adverse effects from investigational product administration.

[redacted]

- Clarify initiation or increase in oral corticosteroid dosing.
- Add Independent Data Monitoring Committee description.
- Administrative, typographical, and formatting changes were made throughout the protocol.

Amendment 2

Protocol Title: A Phase 2b Dose Ranging Study to Evaluate the Efficacy and Safety of Rozibafusp Alfa (AMG 570) in Subjects with Active Systemic Lupus Erythematosus (SLE) with Inadequate Response to Standard of Care (SOC) Therapy

Amgen Protocol Number AMG 570 20170588

Amendment Date: 13 October 2020

Summary of Changes:

- Incorporate changes to the study design to enable the study to support registration, if the results are positive; these changes include:
  - Update study from phase 2 to phase 2b.
  - Revise primary endpoint to SRI-4 response rate at week 52 and make SRI-4 response rate at week 24 a secondary endpoint.
  - Change all key secondary endpoints to secondary endpoints and add secondary disease flare endpoints.

[redacted]

  - Revise statistical methods, including sample size estimate, planned analyses, and efficacy analyses methods for primary and secondary endpoints.
- Clarify options for a subject to proceed in the study if the subject discontinues investigational product prior to week 52.
- Clarify contraceptive guidance and pregnancy and lactation information:
  - Adjust the duration for contraceptive requirements and collection of pregnancy and lactation information to at least 10 additional weeks after the last dose of investigational product for female subjects of childbearing potential.
  - Specify that pregnancy testing should be performed monthly during both the treatment period and at the first 2 safety follow-up visits.
  - Clarify the definition of females of childbearing potential.
- Specify home health care visits will be centrally provided by the sponsor starting at week 22 and will be optional for subjects who have not experienced adverse effects from investigational product administration.

[redacted]

[redacted]

- Clarify initiation or increase in oral corticosteroid dosing.
- Add Independent Data Monitoring Committee description.
- Administrative, typographical, and formatting changes were made throughout the protocol.

Amendment 1

Protocol Title: A Phase 2 Dose Ranging Study to Evaluate the Efficacy and Safety of AMG 570 in Subjects With Active Systemic Lupus Erythematosus (SLE) With Inadequate Response to Standard of Care (SOC) Therapy

Amgen Protocol Number 20170588

Amendment Date: 28 February 2020

Rationale for Major Changes:

- **Remove detectable systemic lupus erythematosus (SLE) standard of care (SOC) drug levels from the inclusion criteria list -** recent evidence of important technical limitations in the methods used to assess levels of those therapies that may lead to a high rate of false negative results (which are particularly significant for some SLE SOC therapies). Therefore, assessments of drug levels of methotrexate, chloroquine and dapsone will be removed from protocol, while assessment of drug levels of hydroxychloroquine, mycophenolate mofetil and azathioprine will remain. Results of those assessments will be used only for exploratory analyses and not for eligibility purposes, as current available evidence is still insufficient to establish a clear correlation between drug levels assessed by the methods used in this protocol and adherence to those therapies.
- **Substitute Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI 2K) by hybrid SLEDAI as part of the efficacy assessment -** hybrid SLEDAI was the SLEDAI version used to validate Systemic Lupus Erythematosus Responder Index (SRI) 4 index *(Navarra et al, 2011; Furie et al, 2011).* The arthritis definition in the hybrid SLEDAI improves the specificity of the instrument for inflammatory arthritis, reducing the probability of false positive scores at baseline and throughout the study.
- **Simplify and reduce screening period -** removal of SLE drug levels from eligibility criteria allows shortening screening period, which simplifies screening process and reduce timelines.
- **Introduce home health care visits -** frequent number of visits to the site (every 2 weeks) has been pointed out by many patients and investigators as a barrier for enrollment. The offer of home care visits is expected to increase study participation.

Rationale for Minor Changes:

- Add Lupus Low Disease Activity State (LLDAS) to key secondary endpoints.
- Reduce period required for oral corticosteroids (OCS) stable dose prior to screening visit - from 4 to 2 weeks.

- Changes to OCS dose permitted between 0 to 4 weeks - from up to 20 mg/day increase in prednisone dose (or equivalent) over baseline to up to 5 mg/day increase (10 mg/day of prednisone or equivalent allowed if OCS being temporarily initiated between 0 to 4 weeks). In both cases, return to baseline dose within 2 weeks is required.
- Remove body surface requirements for rash sore in SLEDAI at screening visit-rash is being evaluated through Cutaneous Lupus Erythematosus Area and Severity Index (CLASI) instrument and there is no need to impose restrictions relatively to the extension of rash (which are difficult to achieve in SLE patients).
- Add language relative to management of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and analgesic therapies throughout the study - Initiation or increases in the NSAIDs or other analgesic therapy dose during the study are allowed if: 1) not initiated within 24 hours of the scheduled monthly efficacy assessments and 2) the subject returns to baseline dose within the subsequent 2 weeks. For patients taking these therapies at baseline, stable dose is recommended throughout the study.
- Substitute FACIT-Fatigue by Patient-Reported Outcome Measurement Information System (PROMIS)-Fatigue scale as part of Patient Reported outcomes (PROs) – PROMIS able to assess impact of fatigue.

[redacted]

- Revise washout period for prior biologic drugs –abatacept 6 months, belimumab and anifrolumab 3 months prior to screening.
- Add additional lab parameters – added CRP, ESR, GGT as part of regular chemistry assessments, add lipid profile (baseline and week 52 only), add [redacted] (baseline, week 24 and 52), add aPTT as part of regular coagulation assessments.