Title Page

Protocol Title:		A Phase 2b Dose Ranging Study to Evaluate the Efficacy and Safety of Efavaleukin Alfa in Subjects with Active Systemic Lupus Erythematosus With Inadequate Response to Standard of Care Therapy (VIOLET)
Short Protocol Title:		Efficacy and Safety of Efavaleukin Alfa in Subjects with Active Systemic Lupus Erythematosus
Protocol Number:		20200234
Investigational Product:		Efavaleukin Alfa
Trade Name:		Not applicable
Sponsor	**Name of Sponsor:**	Amgen Inc.
	Address:	One Amgen Center Drive, Thousand Oaks, CA 91320, USA
	Telephone Number:	+1 (805) 447-1000
Protocol Approver	**Name:**	[redacted], MD
	Function:	Vice President Global Development
Key Sponsor Contact	**Name:**	[redacted], MD
	Address:	One Amgen Center Drive, Thousand Oaks, CA 91320, USA
	Telephone Number:	[redacted]
	Email Address:	[redacted]
EudraCT Number:		2020-003509-72
NCT Number:		NCT04680637
Protocol Version Date:		**Document Version** / **Date** Original / 09 October 2020 Superseding Original Protocol / 30 November 2020 Amendment 1 / 25 August 2021 Amendment 2 / 01 September 2022 Amendment 3 / 21 October 2022 **Amendment 4 / 06 March 2023**
Data Elements Standards Version:		7.0

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

Confidentiality Notice

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the institutional review board/independent ethics committee/institutional scientific review board or equivalent.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1-800-77-AMGEN; Canadian sites, 1-866-50-AMGEN; Amgen's general number in the US, 1-805-447-1000.

Investigator's Agreement:

I have read the attached protocol entitled A Phase 2b Dose Ranging Study to Evaluate the Efficacy and Safety of Efavaleukin Alfa in Subjects with Active Systemic Lupus Erythematosus With Inadequate Response to Standard of Care Therapy (VIOLET), dated **06 March 2023**, 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 subinvestigators (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)

Table of Contents

List of Tables

List of Figures

1. Protocol Summary

1.1 Synopsis

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

Short Protocol Title: Efficacy and Safety of Efavaleukin Alfa in Subjects with Active Systemic Lupus Erythematosus

Study Phase: 2b

Indication: Systemic lupus erythematosus (SLE)

Study Rationale

This is a phase 2b dose-ranging study to assess the efficacy and safety of efavaleukin alfa (AMG 592) in subjects with active SLE. Efavaleukin alfa may be a viable treatment option for SLE patients who are not responding to current standard of care (SOC).

Benefit/Risk Assessment

Based upon the totality of currently available safety data, the benefit/risk profile of efavaleukin alfa is favorable. Efavaleukin alfa has been well tolerated in clinical studies and has an acceptable safety profile. Adverse drug reactions reported with efavaleukin alfa in clinical studies include erythema, pruritus, exacerbation in subjects with rheumatoid arthritis (RA), hypersensitivity, rash, and injection site reaction. Potential risks include cardiovascular, respiratory, hematopoietic, changes in leukocyte population, immunomodulation, immunogenicity, and cytokine release syndrome.

Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• Evaluate the efficacy of efavaleukin alfa at week 52, as measured by the SRI-4 response	• SRI-4 response at week 52
Primary Estimand	
The primary estimand is the difference in SRI-4 response rates between each efavaleukin alfa 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 compliance; subjects will be considered nonresponders for using more than protocol-permitted therapies as follows: • Subjects requiring a dose of systemic corticosteroids for SLE above their baseline dose after week 16 • Subjects requiring either dose increases of the current immunosuppressants/immunomodulators or initiation of new immunosuppressant/immunomodulator(s)	
Secondary	
• Evaluate the efficacy of efavaleukin alfa at week 52, as measured by the BICLA index responses	• BICLA response at week 52
• Evaluate the efficacy of efavaleukin alfa at week 52, as measured by LLDAS response	• LLDAS response at week 52
• Evaluate the efficacy of efavaleukin alfa at week 52, as measured by OCS tapering	• 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 efavaleukin alfa at week 24, as measured by SRI-4 response	• SRI-4 response at week 24
• Evaluate the efficacy of efavaleukin alfa at week 24, as measured by the BICLA index responses	• BICLA response at week 24
• Evaluate the efficacy of efavaleukin alfa at weeks 24 and 52, as measured by hSLEDAI	• hSLEDAI response (ie, reduction ≥ 4 points from baseline) at week 24 • hSLEDAI response (ie, reduction ≥ 4 points from baseline) at week 52

• Evaluate the efficacy of efavaleukin alfa on joints and skin	• Improvement from baseline in tender and swollen joint count ≥ 50% at weeks 8, 12, 24, 36, and 52 in subjects with ≥ 6 tender and swollen joints in hands and wrists • Improvement from baseline in CLASI activity score ≥ 50% at week**s** 8, 12, 24, 36, and 52 in subjects with a CLASI activity score ≥ 8 at baseline
• Evaluate the efficacy of efavaleukin alfa using BILAG score	• 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 efavaleukin alfa using patient reported outcomes	• Change from baseline in fatigue standardized score using the PROMIS Fatigue SF 7a at week**s** 12, 24, 36, and 52 • Change from baseline in the physical component score, mental component score and individual domains of the SF 36 v2 at week**s** 12, 24, 36, and 52 • Change from baseline in the domain scores on the Lupus QoL at weeks 12, 24, 36, and 52
• Characterize the safety of efavaleukin alfa	• Treatment-emergent adverse events • Serious adverse events • Clinically significant changes in laboratory values and vital signs
• Characterize the PK of efavaleukin alfa	• Trough and sparse postdose serum concentrations of efavaleukin alfa

BICLA = British Isles Lupus Assessment Group Based Composite Lupus Assessment; BILAG = British-Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Area and Severity Index ; hSLEDAI = Hybrid Systemic Lupus Erythematosus Disease Activity Index; IL-2 = interleukin-2; LLDAS = Lupus Low Disease Activity State; OCS = oral corticosteroid; PGA = Physician Global Assessment; PK = pharmacokinetic(s); PROMIS Fatigue SF7A = Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a Instrument; QoL = quality of life; SLE= systemic lupus erythematosus; SF36v2 = Medical Outcomes Short Form 36 version 2 Questionnaire; SOC = standard of care; SRI-4 = Systemic Lupus Erythematosus Responder Index; [redacted]

Overall Design

This is a Bayesian adaptive phase 2b, multi-center, double-blind, randomized, placebo-controlled 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.

The study design includes 3 active efavaleukin alfa treatment groups [redacted] every 2 weeks [Q2W], [redacted] Q2W, and [redacted] Q2W) and a placebo group, SRI-4 response at week 52 as the primary endpoint, and an approximate sample size of 320 subjects.

Subjects will be randomized to receive either placebo or 1 of 3 doses of efavaleukin alfa for a duration of 52 weeks. The randomization ratio will start as 1:1:1:1, and then may be adapted at planned interim analyses (IAs) based on the clinical efficacy, as measured by SRI-4 response, using Response Adaptive Randomization (RAR) for the purpose of allocating more subjects to more efficacious doses and fewer subjects to less efficacious doses, with a fixed 25% of subjects allocated to placebo throughout the study. The RAR will be implemented with a computerized system that assigns a treatment to subjects without unblinding any study personnel or Amgen study team members, including the investigators or subjects, to the subject's randomized treatment assignment or the current allocation ratio.

Study duration for a single subject will be 56 weeks (including the safety follow-up period) plus the screening period. Treatment will be administered every 2 weeks with the final dose at week 50. All subjects will be followed for safety for at least 6 weeks after the last dose of investigational product.

Subjects will undergo a screening visit to confirm eligibility requirements. At day 1 (baseline), prior to randomization, disease activity (clinical hybrid SLEDAI score ≥ 4) and stability and compliance of OCS and other immunosuppressant/immunomodulator doses, must be present and confirmed by the investigator. The maximum time between screening and randomization is 33 days. Subjects who do not meet all the eligibility requirements prior to randomization on day 1 will be considered screen failures. Subjects may be allowed to rescreen up to 3 times.

Immunosuppressant/immunomodulator dose(s) should remain stable through week 52. For OCS, initiation or temporary increases in OCS are allowed between weeks 0 to 10, provided that return to baseline dose occurs within the subsequent 2 weeks. Oral corticosteroids may be tapered after week 12 at the investigator's discretion but should not be changed during the last 8 weeks (week 44 to 52) of the 52-week treatment period.

Subjects that use more than protocol-permitted therapies will be allowed to continue the study but will be considered as experiencing treatment failure for the primary efficacy endpoint analyses as specified in the primary estimand.

Interim analyses will be conducted to allow for adaption of the randomization ratio for newly enrolled subjects to the 3 efavaleukin alfa 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 results of the IAs unless futility is determined.
- The first IA will be executed after the first 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 or until futility is determined for all doses at an IA. 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'. Analyses planned at each IA are listed in Table 1-1.
- Efficacy analyses will be performed at the IAs to assess the likelihood of each efavaleukin alfa treatment group being superior to placebo by a clinically meaningful difference.
  - From the second IA until before the last IA, if this likelihood is unacceptably low for all dose levels, the trial is recommended to stop for futility.
  - At the 'all-subjects-week-24 IA', if this likelihood is sufficiently high with at least 1 efavaleukin alfa dose level, this IA will trigger an administrative success signal. This would not alter the ongoing or planned activities of this phase 2b study, but downstream planning for subsequent trials (eg, a phase 3 study) may commence.

Adaptive Design Elements:

The prospectively defined adaptive features include RAR, early decision for futility and an early administrative trigger for success. Adaptations are based on the results of IAs:

- Adaptive randomization begins after a fixed allocation period. After each IA before the 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 at the second and subsequent IAs. If futility is triggered, the study may be terminated, eg, continued enrollment and follow-up activities for previously enrolled subjects could be stopped.
- Efficacy is assessed against predefined rules for administrative success only at the last IA (ie, all-subjects-week-24 IA). If administrative success is determined, downstream activities may be planned/initiated (eg, a phase 3 study), but the execution of this phase 2b trial would not be stopped or altered.
- All adaptive decisions will be based on the SRI-4 response at week 52 with longitudinal modeling of SRI-4 response data. For a subject who has not yet completed through week 52, their 52-week value will be imputed using a longitudinal model based on their week 16, 20, or 24 SRI-4 response data, whichever is the latest.

Modeling and simulations are used to design this Bayesian adaptive trial and refine study design features to achieve optimal operating characteristics.

Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Section 1.3).

Number of Subjects

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

Summary of Subject Eligibility Criteria

Eligible subjects must be between the ages of 18 to 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 **or positive anti-double stranded DNA (anti-dsDNA) antibodies or positive anti-Smith** at screening **per central laboratory assessment**. In addition, at screening, subjects must have a Hybrid Systemic Lupus Erythematosus Disease Activity Index (hSLEDAI) ≥ 6 points and a clinical hSLEDAI ≥ 4 points. Subjects must be taking ≥ 1 of the following SLE treatments (or regional equivalent): mycophenolate mofetil, azathioprine, methotrexate, hydroxychloroquine, chloroquine, dapsone, quinacrine, oral calcineurin inhibitors, or OCS. A subject may enter the study on OCS alone (prednisone ≥ 10 mg/day or equivalent) only if the subject has previously documented trial of anti-malarial or immunosuppressant treatment for SLE. Subjects must be on a stable dose for ≥ 8 weeks prior to screening for all antimalarials and immunosuppressants, with the exception of OCS doses which must be stable for ≥ 2 weeks prior to screening.

Subjects requiring induction therapy for lupus nephritis currently or within 1 year prior to screening or active central nervous system (CNS) lupus within the past year are not eligible for enrollment. Subjects with any disease other than SLE requiring treatment with oral or parenteral corticosteroids for > 2 weeks within 4 months of the screening visit or any clinically significant concurrent medical conditions and/or significant laboratory abnormalities will not be eligible for enrollment (Section 5.2). Female subjects must not be pregnant or breastfeeding or plan to become pregnant or breastfeeding during treatment or for an additional 6 weeks after the last dose of investigational product. **Female subjects of reproductive potential must agree not to donate eggs during the study and for 6 weeks after receiving the last dose of investigational product.**

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

Efavaleukin alfa and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Both are liquid formulations presented in highly similar glass vials and stored in the same manner. Efavaleukin alfa or placebo will be administered by subcutaneous (SC) injection Q2W.

Three efavaleukin alfa dose levels are planned [redacted] Q2W, [redacted] Q2W, and [redacted] Q2W).

Statistical Considerations

The Efficacy Analysis Set including all randomized subjects will be used to perform the efficacy analysis based on subjects' randomized treatment assignment. For safety endpoints, all randomized subjects who received at least 1 dose of investigational product will be analyzed according to the actual treatment received.

At IAs:

- As in Table 1-1, beginning with the second IA until 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% for all 3 efavaleukin alfa doses.
- 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 efavaleukin alfa dose, planning for a phase 3 study may be 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.

At the final analysis,

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

All categorical variables will be summarized using the number and percent of subjects falling into each category, and 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, including incidence of treatment-emergent adverse events and serious adverse events, clinically significant changes in laboratory values and vital signs, and incidence of antidrug antibodies.

Table 1-1. Analyses Schedule
Decisions at Each Interim 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
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 or until futility is determined for all doses at an IA. Number of IAs will depend on the observed 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.

For a full description of statistical analysis methods, please refer to Section 9.

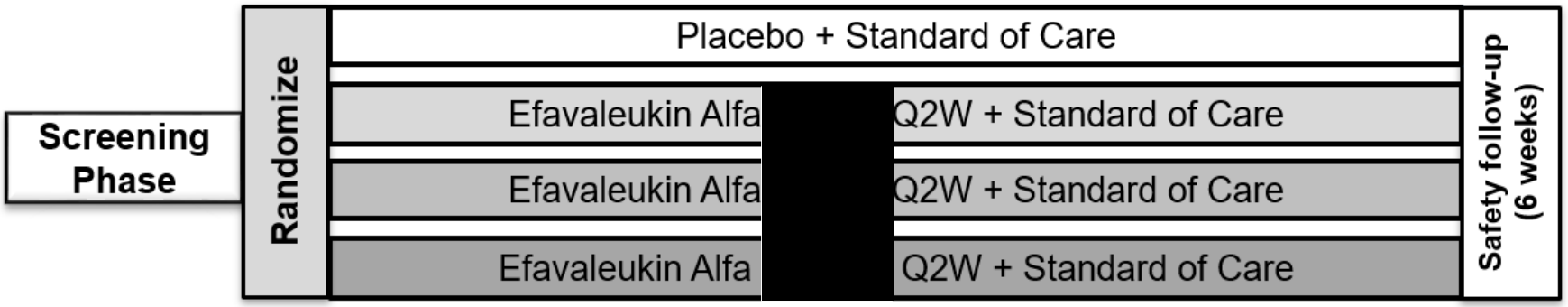
Statistical Hypotheses

At least 1 efavaleukin alfa dose will have greater efficacy than placebo as measured by the SRI-4 response rate at week 52 in subjects with active SLE with inadequate response to SOC therapy who are randomized, regardless of investigational product compliance; subjects using more than protocol-permitted therapies will be considered as nonresponders as specified in the primary estimand.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



Q2W = every 2 weeks

1.3 Schedule of Activities

Table 1-2. Schedule of Activities – Screening and Baseline

DAY	Screening		Baseline		Start of Treatment Period	
	-33 to -1		1		3 to 5	
		Pre-randomization	Predose	Dose	6 to 24 hr postdose	48 to 96 hr postdose
GENERAL AND SAFETY ASSESSMENTS						
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demographics	X					
Physical examination	X		X			
2019 EULAR/ACR classification criteria for SLE	X					
Lupus narrative	X					
Height	X					
Weight	X		X			
Medical history	X					
Substance **use** history	X					
Lupus nephritis history[a]	X					
Vital signs	X	X				
ECG	X					
Adverse events				X →	→	→
Serious adverse events[b]	X →	→	→	→	→	→
Concomitant therapies review	X →	→	→	→	→	→
Randomization[c]			X			
Home health visit[d]					X	X
LABORATORY ASSESSMENTS						
Pregnancy test[e]	X	X				
Tuberculosis screening[f]	X					
HIV, Hepatitis B and C screening[g]	X					
Antinuclear antibody (Hep-2 cells)	X					
Anti-dsDNA[h]	X		X			
Anti-phospholipid antibodies	X		X			
C3 and C4 complements	X		X			
anti-Smith, anti-RNP, anti-SSA/Ro/anti-SSB/La, anti-CCP and rheumatoid factor	X					

Footnotes are presented on last page

Table 1-2. Schedule of Activities – Screening and Baseline

	Screening		Baseline		Start of Treatment Period	
DAY	-33 to -1		1		3 to 5	
		Pre-randomization	Predose	Dose	6 to 24 hr postdose	48 to 96 hr postdose
Coagulation	X					
Thyroid panel	X					
Hematology	X		X			
Chemistry	X		X			
Urinalysis[i] (clean catch)	X		X			
EFFICACY ASSESSMENTS						
Tender/swollen joint count	X		X			
PGA VAS[j]	X		X			
PGA 4-Point Verbal Rating Scale[j]	X		X			
hSLEDAI	X		X			
Clinical hSLEDAI	X	X				
[redacted]						
Prior history of BILAG domains	X					
BILAG	X		X			
CLASI activity and damage	X		X			
[redacted]						
CLINICAL OUTCOME ASSESSMENTS						
SF-36v2			X			
PROMIS-Fatigue SF 7a			X			
LupusQoL			X			
Symptom Questionnaire			X			
[redacted]						
IMMUNOGENICITY						
[redacted]						
BIOMARKER ASSESSMENTS						
[redacted]						
PHARMACOGENETIC ASSESSMENTS						
[redacted]						
PHARMACOKINETIC ASSESSMENTS						
Pharmacokinetic blood sample			X		X[d]	X[d]

Footnotes are presented on last page

Table 1-2. Schedule of Activities – Screening and Baseline

	Screening		Baseline		Start of Treatment Period	
DAY	-33 to -1		1		3 to 5	
		Pre-randomization	Predose	Dose	6 to 24 hr postdose	48 to 96 hr postdose
STUDY TREATMENT						
Investigational product administration[l]				X		

ACR = American College of Rheumatology; anti-CCP = anti-cyclic citrullinated peptide; anti-dsDNA = anti-double stranded DNA; anti-RNP = anti-ribonucleoprotein; anti-SSA/Ro = anti-Sjögren's-syndrome related antigen A; anti-SSB/La = anti-Sjögren's-syndrome related antigen B;; 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; **ECG** = **electrocardiogram;** eCRF = electronic **c**ase **r**eport **f**orm; ET = early termination visit; EULAR = European League Against Rheumatism; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HIV = Human Immunodeficiency Virus; hSLEDAI = Hybrid Systemic Lupus Erythematosus Disease Activity Index; PGA = Physician Global Assessment; [redacted]; PROMIS = Patient Reported Outcomes Measures Information System; [redacted]; SF36v2 = Medical Outcomes Short Form 36 version 2 questionnaire; SLE = systemic lupus erythematosus; SOC = standard of care; VAS = visual analog scale; [redacted]

[a] Only for subjects with a history of lupus nephritis.

[b] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.3.4.1.3 for additional details.

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

[d] Visit may be performed as a home health visit. In addition to collection of pharmacokinetic and [redacted], adverse events, serious adverse events, and concomitant medications review will be conducted.

[e] For women of childbearing potential only: serum pregnancy test is to be performed at screening (central laboratory) and urine pregnancy test is to be performed **prior to randomization** (local laboratory). To determine if follicle-stimulating hormone (FSH) level should be assessed, refer to the definition of postmenopausal female provided in Section 11.5.

[f] Either a centrally performed QuantiFERON®-TB or locally performed purified protein derivative (PPD) or T-spot test will be done during screening. For subjects with a positive tuberculosis test (ie, positive PPD or positive or indeterminate QuantiFERON®-TB or T-spot test) a chest X-ray will be performed.

[g] HIV screening will be performed where allowed by local regulations.

[h] **A subject's anti-dsDNA will be tested with a consistent assay throughout the study.**

[i] Clean catch urine specimen required and urine protein/creatinine ratio will be calculated.

[j] Must be completed by a health care provider before assessing the hSLEDAI and BILAG scores. [redacted]

At visits on which investigational product is administered, all assessments are to be completed in advance of investigational product administration unless otherwise noted. The dose of investigational product must be given within ± 5 days of the scheduled time point. If that window is missed, that dose will not be administered, and the next dose will be administered at the next scheduled dosing date. Any 2 consecutive doses of investigational product must be at least 7 days apart.

Table 1-3. Schedule of Activities – Treatment Period

	Treatment Period (Weeks)																									
WEEK	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[a]
STUDY DAY ± VISIT WINDOW	15 ±5	29 ±5	43 ±5	45 to 47	57 ±5	71 ±5	85 ±5	99 ±5	113 ±5	127 ±5	141 ±5	155 ±5	169 ±5	183 ±5	197 ±5	211 ±5	225 ±5	239 ±5	253 ±5	267 ±5	281 ±5	295 ±5	309 ±5	323 ±5	337 ±5	351 ±5	365 ±5
GENERAL AND SAFETY ASSESSMENTS																										
Physical examination[b]		X			X		X		X		X		X		X		X		X		X		X		X		X
Weight		X			X		X		X		X		X		X		X		X		X		X		X		X
Vital signs	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	←																										→
Serious adverse events[c]	←																										→
Concomitant therapies review	←																										→
Home health visit			X[d]	X[d]																							
LABORATORY ASSESSMENTS																										
Pregnancy test[e]		X			X		X		X		X		X		X		X		X		X		X		X		X
Anti-dsDNA[f]		X			X		X		X		X		X		X		X		X		X		X		X		X
Anti-phospholipid antibodies													X														X
C3 and C4 complements		X			X		X		X		X		X		X		X		X		X		X		X		X
Thyroid panel																											X
Hematology		X			X		X		X		X		X		X		X		X		X		X		X		X
Chemistry		X			X		X		X		X		X		X		X		X		X		X		X		X
Urinalysis[g] (clean catch)		X			X		X		X		X		X		X		X		X		X		X		X		X
EFFICACY ASSESSMENTS																										
Tender/swollen joint count		X			X		X		X		X		X		X		X		X		X		X		X		X
PGA VAS[h]		X			X		X		X		X		X		X		X		X		X		X		X		X
PGA 4-Point Verbal Rating Scale[h]		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
[redacted]																											
BILAG		X			X		X		X		X		X		X		X		X		X		X		X		X
CLASI activity and damage		X			X		X		X		X		X		X		X		X		X		X		X		X
[redacted]																											

Footnotes are presented on last page

Table 1-3. Schedule of Activities – Treatment Period

	Treatment Period (Weeks)																										
WEEK	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[a]
STUDY DAY ± VISIT WINDOW	15 ±5	29 ±5	43 ±5	45 to 47	57 ±5	71 ±5	85 ±5	99 ±5	113 ±5	127 ±5	141 ±5	155 ±5	169 ±5	183 ±5	197 ±5	211 ±5	225 ±5	239 ±5	253 ±5	267 ±5	281 ±5	295 ±5	309 ±5	323 ±5	337 ±5	351 ±5	365 ±5
CLINICAL OUTCOME ASSESSMENTS																											
SF-36v2		X					X						X						X								X
PROMIS-Fatigue SF 7a		X					X						X						X								X
LupusQoL		X					X						X						X								X
Symptom Questionnaire	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
[redacted]																											
IMMUNOGENICITY																											
[redacted]																											
BIOMARKER ASSESSMENTS[i]																											
[redacted]																											
PHARMACOKINETIC ASSESSMENTS																											
Pharmacokinetic blood sample		X[i]	X[j]	X[j]			X[i]						X[i]						X[i]				X[i]				X
STUDY TREATMENT																											
Investigational product[k]	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	

Anti-dsDNA = anti-double stranded DNA; 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 **c**ase **r**eport **f**orm; ET = early termination visit ; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HIV = Human Immunodeficiency Virus; hSLEDAI = Hybrid Systemic Lupus Erythematosus Disease Activity Index; PGA = Physician Global Assessment; [redacted] PROMIS = Patient Reported Outcomes Measures Information System; [redacted] SF36v2 = Medical Outcomes Short Form 36 version 2 questionnaire; SLE = systemic lupus erythematosus; SOC = standard of care; VAS = visual analog scale; [redacted]

[a] An ET is required for all subjects who discontinue the study completely prior to week 52. Please refer to Section 8.1.2.

[b] After initiation of treatment, physical examination is required for all elements relevant to lupus endpoints and/or adverse events.

[c] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.3.4.1.3 for additional details.

[d] On day 43, investigational product administration and assessments which are to be completed prior to investigational product administration, will be completed at the study site. Visit for pharmacokinetic blood sample collection may be performed as a home health visit. In addition to collection of pharmacokinetic blood samples, adverse events, serious adverse events, and concomitant medications review will be conducted.

[e] For women of childbearing potential only: serum pregnancy test is to be performed at screening (central laboratory) and urine pregnancy test is to be performed at all other indicated time points (local laboratory). To determine if follicle-stimulating hormone (FSH) level should be assessed, refer to the definition of postmenopausal female provided in Section 11.5.

[f] **A subject's anti-dsDNA will be tested with a consistent assay throughout the study.**

[g] Clean catch urine specimen required and urine protein/creatinine ratio will be calculated.

[h] Must be completed by a health care provider before assessing the hSLEDAI and BILAG scores.

[i] To be taken predose.

[j] A single pharmacokinetic blood sample will be collected between 6 and 24 hours postdose week 6 and another pharmacokinetic sample will be collected between 48 and 96 hours postdose week 6. These samples may be collected as part of a home health visit.

[k] At visits on which investigational product is administered, all assessments are to be completed in advance of investigational product administration unless otherwise noted. The dose of investigational product must be given within ± 5 days of the scheduled time point. If that window is missed, that dose will not be administered, and the next dose will be administered at the next scheduled dosing date. Any 2 consecutive doses of investigational product must be at least 7 days apart.

Table 1-4. Schedule of Activities – Safety Follow-up/week 56 Visit

	Safety Follow-up Visit (Weeks)
Week ± Visit Window (days)	**56 weeks +5 days[a]**
Vital signs	X
Adverse events	X
Serious adverse events[b]	X
Concomitant medications review	X
LABORATORY ASSESSMENTS	
Urine pregnancy test	X
Hematology	X
IMMUNOGENICITY	
[redacted]	

[a] This separate safety follow-up/week 56 visit only applies to subjects who require an additional visit following the planned 52-week period to ensure at least 6 weeks follow-up for safety data collection after last dose of 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 8.3.4.1.3 for additional details.

2. Introduction

2.1 Study Rationale

This is a phase 2b dose-ranging study to assess the efficacy and safety of efavaleukin alfa (AMG 592) in subjects with active systemic lupus erythematosus (SLE).

2.2 Background

2.2.1 Disease

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

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

2.2.1.1 Interleukin 2 and T Regulatory Cells in Systemic Lupus Erythematosus

T regulatory cells (Tregs) are a subset of T cells that maintain self- tolerance by suppressing the activation and expansion of autoreactive lymphocytes. Defects in Treg numbers or function have been described in SLE patients and are thought to contribute to SLE pathogenesis (Zhang et al, 2018; Bonelli et al, 2009; Myara et al, 2005; Suen et al 2008; von Spee-Mayer et al 2015). Interleukin-2 (IL-2), a multi-functional

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

2.2.1.2 Low Dose Interleukin 2 in Inflammatory Disease

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

The therapeutic efficacy of low dose IL-2 has also been studied in chronic GVHD (cGVHD) (Koreth et al, 2011; Koreth et al, 2016), hepatitis C induced vasculitis (Sadoun et al, 2011), and alopecia areata (Castela et al, 2014). The clinical response to low dose IL-2 has been promising in these small early phase studies in multiple diverse inflammatory conditions, with efficacy reported in various indications. In these conditions, the overall safety and tolerability profile of low-dose IL-2 has been acceptable with mild to moderate constitutional symptoms associated with higher levels of exposure. However, the therapeutic window between adequate Treg enrichment and stimulation of effector cells is narrow and may limit achievement of optimal Treg expansion. For instance, in a recent phase 1b clinical trial of cGVHD (ClinicalTrials.gov NCT00529035), aldesleukin, a human recombinant IL-2, given at the dose of 3 x 106 IU/m2 daily induced persistent National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grade 1 constitutional symptoms (fever, malaise, and arthralgia) necessitating a 50% dose reduction (Koreth et al, 2011). In addition, aldesleukin can activate pro-inflammatory/effector lymphocytes such as CD4+ T effector cells (Teff) and natural killer (NK) cells, which

may compromise efficacy and safety. These data suggest the potential for a therapeutic agent with greater Treg selectivity and a prolonged **pharmacodynamic (**PD**)** effect compared with recombinant IL-2.

2.2.1.3 Clinical experience with Low Dose IL-2 in Systemic Lupus Erythematosus

Treatment with low dose IL-2 has been associated with clinical efficacy in small clinical trials. In **1** placebo-controlled study of 60 patients (30 IL-2; 30 placebo) on standard treatment with active SLE, after 12 weeks of treatment the SRI-4 response rates were 55.17% for the IL-2 group compared to 30.00% for the placebo group (p = 0.052). At week 24 (12 weeks post last dose) the SRI-4 response rate for the IL-2 group was 65.52% compared with 36.67% for the placebo group (p = 0.027). Low-dose IL-2 treatment resulted in 53.85% (7/13) complete remission in patients with lupus nephritis compared with 16.67% (2/12) in the placebo group (p = 0.036) (He et al, 2020).

In a study of 12 patients with moderate to severe SLE (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] score $\geq$ 6 points despite treatment with 2 different immunosuppressive therapies), 10/12 subjects (83.3%) achieved a reduction in SELENA SLEDAI score and 8/12 (66.7%) achieved a clinical response after receiving four 5-day cycles of low dose IL-2 therapy separated by washout periods of 9 and 16 days. Clinical responses included complete resolution of SLE manifestations including rash, arthralgias, myositis and alopecia. Complement levels increased but no change in anti-double stranded DNA (anti-dsDNA) antibodies was observed. Regulatory T cells numbers increased in all treated subjects (Humrich et al, 2019; Humrich et al, 2016; Humrich et al, 2015).

In another study of 38 SLE patients who completed three 2-week cycles of low dose IL-2 over 12 weeks, 34/38 subjects (89.5%) achieved a Systemic Lupus Erythematosus Responder Index 4 (SRI-4) response at the end of 12 weeks, with concomitant decreases in anti-dsDNA antibodies and increase in complement levels. Regulatory T cells numbers increased in most treated subjects (He et al, 2016). In these studies, low dose IL-2 was generally well- tolerated, though constitutional symptoms (eg, fever, myalgias, arthralgias, flu-like symptoms) were reported at the higher dose levels. Overall**,** these studies provide compelling support for further investigation of IL-2 for the treatment of SLE.

2.2.2 Amgen Investigational Product Background: Efavaleukin Alfa

Efavaleukin alfa is an IL-2 mutein Fc fusion protein with increased Treg selectivity compared to recombinant IL-2, which has been developed to preferentially expand Tregs in subjects with inflammatory diseases (refer to the Efavaleukin Alfa Investigator's Brochure for more details). Interleukin-2 is a key growth factor for Tregs and is essential for Treg development, homeostasis and function. At low doses IL-2 binds preferentially to the α-subunit (CD25) of the high-affinity IL-2 receptor which is expressed constitutively by Tregs and is absent on naive T-cells and inactivated T memory cells. This results in selective activation of Tregs. However, at higher doses IL-2 also activates other immune cells such as CD4+ and CD8+ Teff, NK cells and natural killer T cells cells via the dimeric low affinity IL-2 receptor. Compared with aldesleukin, efavaleukin alfa exhibits greatly improved selectivity for Tregs over Teff and NK cells both in vitro and in vivo, potentially resulting in an improved therapeutic margin. In addition, the Fc domain of efavaleukin alfa provides a prolonged half-life compared with aldesleukin, thus reducing dosing frequency to maintain Treg enrichment (Tchao, 2019).

2.2.2.1 Toxicology

In the 6-month repeat-dose toxicology studies in the cynomolgus monkey (dose levels 0.03 and 0.1 mg/kg, weekly subcutaneous [SC] injections for 6 months), the no observed adverse effect level (NOAEL) dose was 0.03 mg/kg based on the observation of 2 efavaleukin alfa-related unscheduled euthanasia at 0.1 mg/kg associated with moribund condition and markedly decreased RBC mass. The NOAEL of 0.03 mg/kg corresponded to a mean efavaleukin alfa maximum observed concentration (C_{max}) of 130 ng/mL (day 176) and an area under the concentration-time curve from time 0 to 168 hours (AUC_{last}) of 10 300 hr•ng/mL (day 176) in animals that maintained exposure. For further details regarding efavaleukin alfa toxicology studies, please refer to the Investigator's Brochure.

2.2.2.2 Human Exposure

The observed efavaleukin alfa human exposures from single ascending doses of efavaleukin alfa ranging from [redacted] in the first in human (FIH) study 20140324 in healthy subjects and all available **pharmacokinetic (**PK**)** data up to [redacted] from 3 phase 1b studies (20170103 in subjects with SLE; 20170149 in subjects with RA; and 20160283 in subjects with cGvHD) were used to predict efavaleukin alfa exposures at the selected dose levels for the current study in subjects with SLE (Table 2-1). The

geometric mean C_{max} and AUC_{inf} increase approximately dose proportionally over the dose range of [redacted] The estimated terminal phase half-life ranges from about 10.6 to 30.4 hours. Given the estimated half-life, minor accumulation of efavaleukin alfa is expected at the selected dose levels with Q2W dosing regimens in patients with SLE.

Table 2-1. Steady-state Median (IQR) of Efavaleukin Alfa Pharmacokinetic Parameter Prediction Following Q2W Subcutaneous Doses in Subjects with SLE

Dose [redacted]	AUC_{ss} (day•ng/mL)	C_{max} (ng/mL)
[redacted] Q2W	11.75 (8.18 - 16.20)	9.30 (7.55 - 11.47)
Q2W	22.88 (15.87 - 32.27)	18.91 (14.96 - 23.16)
Q2W	43.10 (29.92 - 60.31)	34.84 (27.81 - 43.10)

AUC_{ss} = area under the serum concentration curve at steady state; C_{max} = maximum observed concentration; IQR = interquartile range; Q2W = every 2 weeks; SLE= systemic lupus erythematosus

A detailed description of the chemistry, pharmacology, and safety of efavaleukin alfa is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

The safety of efavaleukin alfa has been evaluated in healthy subjects and **p**hase 1 studies of subjects with RA, cGvHD, and SLE. Cumulative data from completed and ongoing **p**hase 1 clinical studies conducted since the beginning of the development program through 26 April 2022 include 167 subjects who have been exposed to at least 1 dose of efavaleukin alfa. Single doses of up to [redacted] μg have been studied in healthy subjects (82 subjects). Repeated doses of up to [redacted] Q2W have been evaluated in subjects with RA over the course of a 12-week period (28 subjects). Repeated doses of up to [redacted] Q2W have been evaluated in subjects with cGvHD over a 52-week period (32 subjects). Repeated doses of up to [redacted] Q2W have been evaluated in subjects with SLE over a 12-week treatment period (25 subjects).

Based upon the totality of currently available safety data, the benefit/risk profile of efavaleukin **alfa** is favorable. Efavaleukin **alfa** has been well tolerated in clinical studies and has an acceptable safety profile. Adverse drug reactions reported with efavaleukin alfa in clinical studies include erythema, pruritus, exacerbation in subjects with RA, hypersensitivity, rash, and injection site reaction. Potential risks include cardiovascular, respiratory, hematopoietic, changes in leukocyte population, immunomodulation, immunogenicity, and cytokine release syndrome. The most frequent adverse events

have been mild or moderate (grade 1 or 2) injection site reactions, erythema, pruritis, and rash. More information about the safety profile of efavaleukin alfa may be found in the latest version of the Investigator's Brochure.

2.3.1 COVID-19

Amgen closely monitors the coronavirus disease 2019 (COVID-19) pandemic around the world. As part of this effort, Amgen performs a rigorous assessment, considering the study design, patient safety, public health risk, benefit-risk assessment, as well as the burden on country healthcare systems. Decisions are made on a study-by-study and country-by-country basis to minimize risk to subjects and avoid undue burden on healthcare facilities.

Subjects who display symptoms consistent with COVID-19 infections or who have tested positive for COVID-19 should contact the investigator to ensure appropriate care as well as documentation and management of study activities. Amgen considers that it is important to continue the proposed development of efavaleukin alfa in this study in order to advance potential therapy options for patients as rapidly as possible, while balancing this with appropriate measures to monitor and mitigate the potential impact of COVID-19. Subjects enrolled in this study are permitted to receive vaccinations for COVID-19 except as described in exclusion criterion 220 and Section 6.1.6.

3. Objectives and Endpoints/Estimands

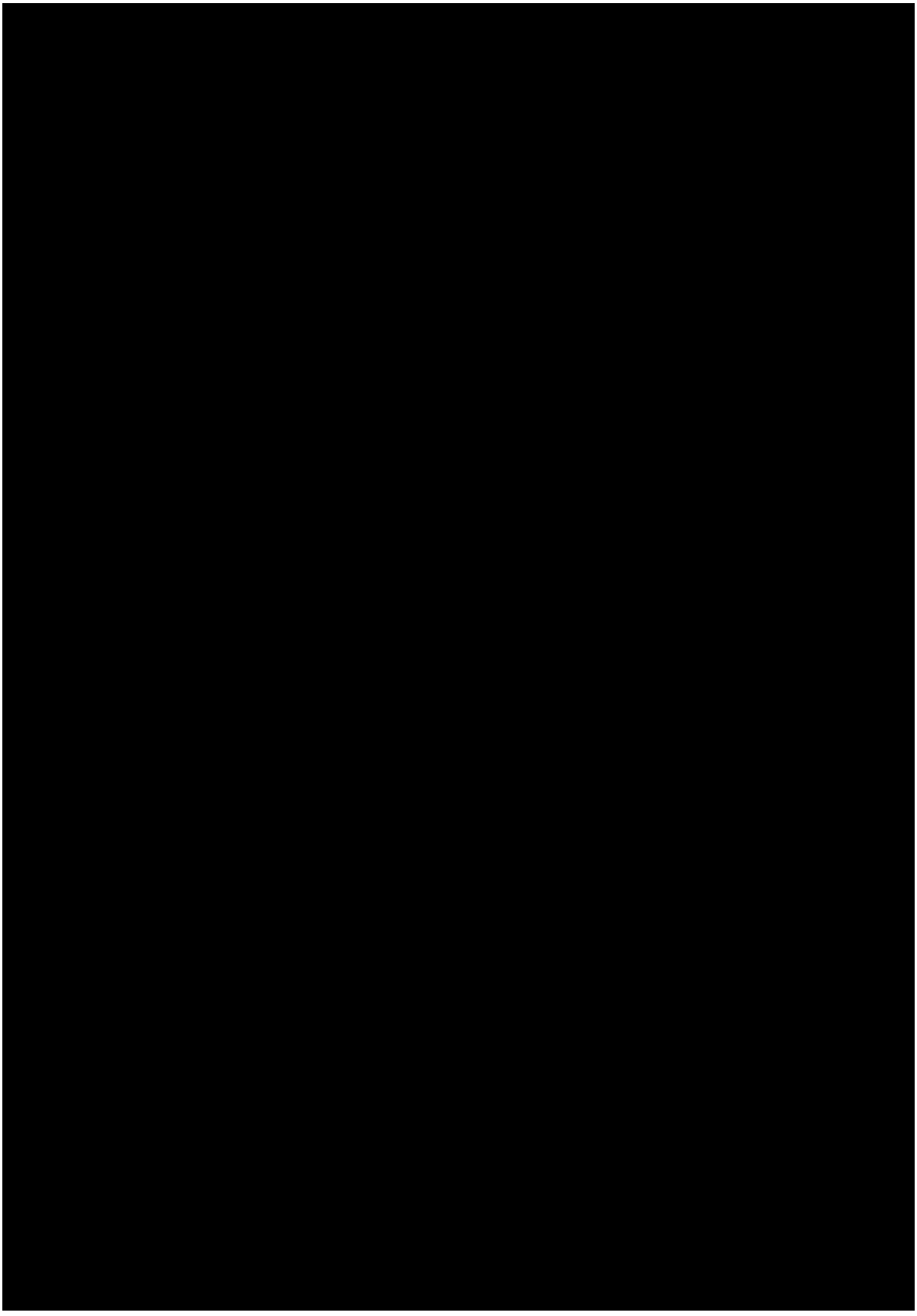
Objectives	Endpoints
Primary	
• Evaluate the efficacy of efavaleukin alfa at week 52, as measured by the SRI-4 response	• SRI-4 response at week 52
Primary Estimand	
The primary estimand is the difference in SRI-4 response rates between each efavaleukin alfa dose group and placebo at week 52 for all subjects with SLE with inadequate response to SOC therapy who are randomized, regardless of investigational product compliance; subjects will be considered nonresponders for using more than protocol-permitted therapies as follows: • Subjects requiring a dose of systemic corticosteroids for SLE above their baseline dose after week 16 • Subjects requiring either dose increases of the current immunosuppressants/immunomodulators or initiation of new immunosuppressant/immunomodulator(s)	
Secondary	
• Evaluate the efficacy of efavaleukin alfa at week 52, as measured by the BICLA index responses	• BICLA response at week 52
• Evaluate the efficacy of efavaleukin alfa at week 52, as measured by LLDAS response	• LLDAS response at week 52
• Evaluate the efficacy of efavaleukin alfa at week 52, as measured by OCS tapering	• 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 efavaleukin alfa at week 24, as measured by SRI-4 response	• SRI-4 response at week 24
• Evaluate the efficacy of efavaleukin alfa at week 24, as measured by the BICLA index responses	• BICLA response at week 24
• Evaluate the efficacy of efavaleukin alfa at weeks 24 and 52, as measured by hSLEDAI	• hSLEDAI response (ie, reduction ≥ 4 points from baseline) at week 24 • hSLEDAI response (ie, reduction ≥ 4 points from baseline) at week 52

• Evaluate the efficacy of efavaleukin alfa on joints and skin	• Improvement from baseline in tender and swollen joint count ≥ 50% at weeks 8, 12, 24, 36, and 52 in subjects with ≥ 6 tender and swollen joints in hands and wrists • Improvement from baseline in CLASI activity score ≥ 50% at week**s** 8, 12, 24, 36, and 52 in subjects with a CLASI activity score ≥ 8 at baseline
• Evaluate the efficacy of efavaleukin alfa using BILAG score	• 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 efavaleukin alfa using patient reported outcomes	• Change from baseline in fatigue standardized score using the PROMIS Fatigue SF 7a at week**s** 12, 24, 36, and 52 • Change from baseline in the physical component score, mental component score and individual domains of the SF 36 v2 at week**s** 12, 24, 36, and 52 • Change from baseline in the domain scores on the Lupus QoL at weeks 12, 24, 36, and 52
• Characterize the safety of efavaleukin alfa	• Treatment-emergent adverse events • Serious adverse events • Clinically significant changes in laboratory values and vital signs
• Characterize the PK of efavaleukin alfa	• Trough and sparse postdose serum concentrations of efavaleukin alfa

BICLA = British Isles Lupus Assessment Group Based Composite Lupus Assessment; BILAG = British-Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Area and Severity Index ; hSLEDAI = Hybrid Systemic Lupus Erythematosus Disease Activity Index; IL-2 = interleukin-2; LLDAS = Lupus Low Disease Activity State; OCS = oral corticosteroid; PGA = Physician Global Assessment; PK = pharmacokinetic(s); PROMIS Fatigue SF7A = Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a Instrument; QoL = quality of life; SLE= systemic lupus erythematosus; SF36v2 = Medical Outcomes Short Form 36 version 2 Questionnaire; SOC = standard of care; SRI-4 = Systemic Lupus Erythematosus Responder Index; [redacted]

Exploratory

[redacted]



4. Study Design

4.1 Overall Design

This is a Bayesian adaptive phase 2b, multi-center, double-blind, randomized, placebo-controlled 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.

The study design includes 3 active efavaleukin alfa treatment groups [redacted] Q2W, [redacted] Q2W, and [redacted] Q2W) and a placebo Q2W group, SRI-4 response at week 52 as the primary endpoint, and an approximate sample size of 320 subjects.

Subjects will be randomized to receive either placebo or 1 of 3 doses of efavaleukin alfa for a duration of 52 weeks. The randomization ratio will start as 1:1:1:1, and then may be adapted at planned interim analyses (IAs) based on the clinical efficacy, as measured by SRI-4 response, using Response Adaptive Randomization (RAR) for the purpose of allocating more subjects to more efficacious doses and fewer patients to less efficacious doses. The RAR will be implemented with a computerized system that assigns a treatment to subsequent subjects without unblinding any study personnel or Amgen study team members including the investigators or subjects, the subject's randomized treatment assignment or the current allocation ratio.

Study duration for a single subject will be 56 weeks (including safety follow-up) plus the screening period. Treatment will be administered every 2 weeks with the final dose at week 50. All subjects will be followed for safety for at least 6 weeks after the last dose of investigational product.

Subjects will undergo a screening visit to confirm eligibility requirements. At day 1 (baseline), prior to randomization, disease activity (defined by clinical hybrid SLEDAI score ≥ 4) and stability and compliance of OCS and other immunosuppressant/immunomodulator doses, must be present and confirmed by the investigator. Subjects may be randomized at any time after confirmation of all eligibility criteria, but the maximum time between screening and randomization is 33 days. Subjects who do not meet all the eligibility requirements at day 1 will be considered screen failures. Subjects may be allowed to rescreen up to 3 times.

Immunosuppressant/immunomodulator doses should remain stable through week 52. For OCS, initiation or temporary increases in OCS are allowed between weeks 0 to 10, provided that return to baseline dose occurs within the subsequent 2 weeks. Oral corticosteroids may be tapered after week 12 at the investigator's discretion but should not be changed during the last 8 weeks (week 44 to 52) of the 52-week treatment period.

Subjects that use more than protocol-permitted therapies will be allowed to continue the study but will be considered as experiencing treatment failure for the primary efficacy endpoint analyses as specified in the primary estimand.

Interim analyses will be conducted to allow for adaption of the randomization ratio for newly enrolled subjects to the 3 efavaleukin alfa 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 results of the IAs unless futility is determined.
- The first IA will be executed after the first 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 or until futility is determined for all doses at an IA. The last IA, referred to as 'all-subjects-week-24 IA' will occur when all 320 subjects are randomized and have had the opportunity to complete the week 24 assessment. Analyses planned at each IA are listed in Table 1-1.
- Efficacy analyses will be performed at the IAs to assess the likelihood of efavaleukin alfa treatment group being superior to placebo by a clinically meaningful difference.
  - From the second IA until before the last IA, if this likelihood is unacceptably low for all dose levels, the trial is recommended to stop for futility.
  - At the 'all-subjects-week-24 IA', if this likelihood is sufficiently high with at least 1 efavaleukin alfa dose level, IA triggers an administrative success signal. This would not alter ongoing or planned activities of this phase 2b study, but downstream planning for subsequent trials (eg, a phase 3 study) may commence.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

4.1.1 Adaptive Design Elements

The prospectively defined adaptive features include RAR, early decision for futility and an early trigger for administrative success. Adaptations are based on the results of IAs:

- Adaptive randomization begins after a fixed allocation period. After each IA before the 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 (see Section 9.3.1.1) at the second and subsequent IAs. If futility is triggered, the study may be terminated, eg, continued enrollment and follow-up activities for previously enrolled subjects could be stopped.
- Efficacy is assessed against predefined rules for administrative success (see Section 9.3.1.1) only at the last IA (ie, all-subjects-week-24 IA). If administrative success is determined, downstream activities may be planned/initiated (eg, a phase 3 study), but the execution of this phase 2b trial would not be stopped or altered.
- All adaptive decisions will be based on the SRI-4 response at week 52 with longitudinal modeling SRI-4 response data. For a subject who has not yet completed through 52 weeks, their 52-week value will be imputed using a longitudinal model based on their week 16, 20, or 24 SRI-4 response data, whichever is the latest.

Modeling and simulations are used to design this Bayesian adaptive trial and refine study design features to achieve optimal operating characteristics.

4.2 Patient Input into the Study Design

Patient input was not obtained for design of this study.

4.3 Justification for Investigational Product Dose

Efavaleukin alfa has demonstrated an acceptable safety and tolerability profile as well as pharmacodynamic selectivity ([redacted]) in subjects with SLE at doses up to [redacted] Q2W for 12 weeks. A higher dose of [redacted] Q2W was also safe and well-tolerated although results suggest a plateau in Treg expansion with low-level increases in other IL-2-responsive cells. Interpretation of these data is limited due to small subject numbers.

Three doses of [redacted] Q2W were selected for this phase 2b study with a predicted upper range of Treg expansion close to 5-, 7-, and 10- fold respectively. These doses provide an opportunity to test a wide range of Treg expansion to help select an efficacious dose.

The low dose of [redacted] Q2W was selected because the mean Treg expansion at this dose level was statistically different from the placebo group in the phase 1b study of efavaleukin alfa in SLE subjects. Also, Treg expansion at the [redacted] Q2W dose appears comparable to Treg expansion associated with clinical efficacy in studies of low dose IL-2 in SLE patients, as reported by Humrich et al, 2019 and He et al, 2020.

However, this comparison may not be accurate due to the methodological differences between studies in efavaleukin alfa and these publications.

A high dose of [redacted] Q2W was selected for the phase 2 study based on predicted Treg expansion with sustained pharmacodynamic selectivity that is substantially higher than the [redacted] Q2W dose and on average higher than [redacted] Q2W dose, thus providing wide range of Treg expansion. In addition, the [redacted] Q2W dose has been tested in subjects with cGVHD for up to 52 weeks with, acceptable safety, sustained pharmacodynamic selectivity, and increased mean Treg expansion compared to other doses.

The middle dose of [redacted] Q2W was selected to minimize the overlap in predicted Treg expansion between the low and high doses.

The predicted Treg expansion was determined by integrated PK/Treg modeling using all available PK and Treg data from phase 1 studies in both healthy subjects and subjects with RA, cGvHD and SLE. Simulations from the PK/Treg model predicted meaningful Treg expansion in subjects with SLE at all selected doses with an expected difference in median Treg cell count between doses (Table 4-1).

Table 4-1. Median (IQR) Peak Blood Treg Count and Fold Expansion Predicted at Planned Doses in Subjects with SLE

Dose [redacted]	Peak Treg expansion Cell Count (Cells/µL)	Peak Treg expansion Fold-Change from Baseline
[redacted] Q2W)	196.66 (126.55 – 283.67)	3.92 (2.97 – 5.21)
[redacted] Q2W)	272.43 (180.79 – 355.27)	5.14 (3.92 – 6.92)
[redacted] (Q2W)	349.13 (264.91 – 427.55)	6.81 (5.23 – 9.28)

Treg = regulatory T cells; Q2W = every other week; IQR = interquartile range

4.4 End of Study

An individual subject is considered to have completed the study if they have remained on study for the entire treatment period (ie, through the week 52 visit) and completed the safety follow-up/week 56 visit (if applicable, see Table 1-4).

The end of study date for the entire 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), including any additional parts in the study (eg, safety follow-up, additional antibody testing), as applicable.

5. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Response Technology (IRT) system. Eligibility criteria will be evaluated at the screening visit and at the baseline/day 1 visit, prior to randomization.

The screening visit will confirm all eligibility requirements described in Inclusion Criteria 101 through 110. For France, affiliation to a social security scheme is required (criterion 111). All SLE-related screening criteria will be reviewed by the adjudication team.

Eligibility Adjudication

Adjudication committee description: An Adjudication Committee composed of medically-qualified SLE experts will be utilized to confirm eligibility during screening and will be utilized throughout the study to confirm Hybrid Systemic Lupus Erythematosus Disease Activity Index (hSLEDAI), BILAG-2004, Cutaneous Lupus Erythematosus Area and Severity Index (CLASI), joint count, [redacted], Physician Global Assessment (PGA), and Systemic Lupus International Collaborating Clinics (SLICC) damage index. The Adjudication Committee will also ensure that the completion of efficacy assessments by investigators is of proper quality and consistency.

The Adjudication Committee will adjudicate eligibility for this trial. During screening, the Adjudication Committee will confirm eligibility criteria are met based on review of the data captured in the electronic data capture (EDC) system and from the central laboratory. The Adjudication Committee will review all data necessary to characterize subject's SLE including past medical history, concomitant medications, 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria, lupus narrative, hSLEDAI, BILAG-2004, 28-joint count, CLASI, and central laboratory results. Sites will be notified of the external SLE Adjudication Committee's decision on whether the subject can proceed to baseline/day 1 visit or to screen fail the subject.

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 8.1.1.

The baseline/day 1 visit will occur within 33 calendar days following the screening visit. At the baseline/day 1 visit subjects will be assessed for Inclusion Criteria 108 and 109 prior to randomization. Subjects who meet all eligibility criteria may proceed to randomization and dosing.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

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

Post-randomization Adjudication

The Adjudication Committee will assist in the ongoing review of data and adjudication of this trial including all clinical reported outcome assessments. The group will remain blinded for the duration of the study.

If there is inconsistency between assessments, additional clarification and training on these assessments will be provided.

5.1 Inclusion Criteria

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

Inclusion Criteria - Screening Visit

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

102 Age ≥ 18 years to 75 years at screening.

103 Fulfills classification criteria for SLE according to the 2019 EULAR/ACR classification criteria for SLE (Aringer et al, 2019), with antinuclear antibody ≥ 1:80 by immunofluorescence on Hep-2 cells **or positive anti-dsDNA antibodies or positive anti-Smith** at screening **per central laboratory assessment**.

110 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 and immunologic parameters. Including the following protocol specific rules:

- Arthritis: for hSLEDAI scoring purposes, a minimum of 3 joints with pain and signs of inflammation (ie, tenderness with swelling or effusion) must involve small joints in the hands, wrists, or a combination of joints in hands and wrists.
- Alopecia: subjects should have active 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 < 2000 mg/g (or equivalent) in a clean catch spot urine sample can enroll and be scored in the hSLEDAI, provided the subject has a clinical hSLEDAI ≥ 4.
- Pleurisy and Pericarditis: symptoms of pleurisy and pericarditis must be accompanied by objective findings to be scored in the hSLEDAI.

105 BILAG index score (BILAG 2004) of ≥ 1 A item or ≥ 2 B items.

106 Must be taking ≥ 1 of the following SLE treatments (or regional equivalent): hydroxychloroquine, chloroquine, quinacrine, mycophenolate mofetil, azathioprine, methotrexate, dapsone, or oral calcineurin inhibitors, or OCS. A subject may enter the study on OCS alone (prednisone ≥ 10 mg/day or equivalent) only if the subject has previously documented trial of anti-malarial or immunosuppressant treatment for SLE. Subjects must be on a stable dose for ≥ 8 weeks prior to screening for all antimalarials and immunosuppressants, with the exception of OCS doses which must be stable for ≥ 2 weeks prior to screening.

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

111 For France, affiliation to a social security scheme is required.

Inclusion Criteria - Day 1 (Baseline)

The baseline/day 1 visit should occur after confirmation of eligibility by the adjudication team within 33 days after the screening visit. At the baseline/day 1 visit, the following 2 criteria should be assessed prior to randomization:

108 Stability of SLE treatments: OCS and other immunosuppressants/immunomodulator agents and doses must be stable since screening visit.

109 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 including urine and immunologic parameters).

5.2 Exclusion Criteria

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

Disease Related

231 Lupus nephritis if any of the following are present:

- urine protein creatinine ratio ≥ 2000 mg/g (or equivalent) at screening, OR
- requiring induction therapy currently or within 1 year prior to screening, OR
- histological evidence (if available) of diffuse proliferative glomerulonephritis within 12 weeks prior to screening.

202 Active **central nervous system (**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

232 Currently present or within 1 year prior to screening a diagnosis of any chronic inflammatory disease other than SLE (eg, **presence of anti-cyclic citrullinated peptide [anti-CCP] and rheumatoid factor OR current history of RA OR presence of erosive arthritis on imaging**) which would interfere with SLE disease assessment.

204 History of any disease other than SLE that has required treatment with oral or parenteral corticosteroids for > 2 weeks within 4 months prior to screening.

205 Active infection (including chronic or localized infections) currently or within **2** weeks prior to screening visit OR presence of serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to screening visit.

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

207 Positive test for **TB** during screening defined as: either a 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 and negative chest X-ray.
- 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 **TB** 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 **TB** after most recent treatment/prophylaxis.
- chest X-ray with no new radiographic findings suggestive of active TB (to be read by local facility).

Note: For criterion 207, 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/exposure history suggests newly acquired infection or recent contact with TB cases and repeat testing of an indeterminate QuantiFERON®-TB test using the T spot test may be performed.

233 Positive for hepatitis B surface antigen (HBsAg); or positive for hepatitis B core antibody (HBcAb). A positive hepatitis B surface antibody (HBsAb) without history of hepatitis B infection (ie, positive HBsAb, negative HBsAg and negative HBcAb) is allowed.

234 Positive for hepatitis C antibody.

210 Known history of HIV or positive HIV test at screening.

Note: For criteria 233, 234, and 210, these tests do not need to be repeated at the time of rescreening, unless re-screening occurs ≥ 12 months from screening or there is evidence or suspicion of recent infection.

235 Presence of 1 or more significant concurrent medical conditions, including but not limited to the following:

- Poorly controlled diabetes (hemoglobin A1C > 7) 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.

Note: For criterion 235, 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.

212 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 breast ductal carcinoma in situ > 5 years of screening.

Prior/Concomitant Therapy

213 Currently receiving or had treatment with: cyclophosphamide, chlorambucil, nitrogen mustard, or any other alkylating agent within 6 months prior to screening or sirolimus within 4 weeks prior to screening.

237 Currently receiving or had treatment with a Janus kinase (JAK) inhibitor **or tyrosine kinase (TYK) inhibitor** within less than 5 drug half-lives prior to screening.

215 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.

216 Currently receiving or had treatment within 12 months prior to screening with T-cell depleting agents (eg, antithymocyte globulin, Campath).

217 Currently receiving or had treatment with an IL-2 based therapy (eg, Proleukin).

238 Current or previous treatment with a biologic agent with immunosuppressive/immunomodulatory activity as follows: rituximab within 6 months prior to screening; abatacept, belimumab, and anifrolumab within the past 3 months prior to screening; other biologics within $<$ 5 drug half-lives prior to screening.

219 Subjects who have received intraarticular, intralesional, or intramuscular corticosteroids within 2 weeks prior to screening or intravenous corticosteroids within 6 weeks prior to screening.

220 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 6 weeks after the end of treatment period in the study.

Prior/Concurrent Clinical Study Experience

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

222 Ending a treatment with an investigational drug or investigational device less than 3 months or 5 half-lives from the last dose of the investigational drug (whichever is longer) at screening.

Diagnostic Assessments

236 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) ≥ 1.5 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 $<$ 50 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula.

224 Any other laboratory abnormality, which in the opinion of the investigator, 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

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

239 Female subjects of reproductive potential must agree not to donate eggs during the study and for 6 weeks after receiving the last dose of investigational product.

226 Female of childbearing potential with a positive pregnancy test (assessed by a serum pregnancy test at screening and a urine pregnancy test **prior to randomization**).

227 Female subject of childbearing potential unwilling to use 1 highly effective method of contraception (see Section 11.5) during treatment and for an additional 6 weeks after the last dose of investigational product.

228 Subject has known sensitivity to any products to be administered during dosing.

229 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.

230 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

5.3 Lifestyle Considerations

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

5.4 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 and/or recruitment material, as applicable (see Section 11.3).

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 subject has met all eligibility criteria (including criteria at the screening visit and the baseline/day 1 visit) and has subsequently been randomized. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF). At the baseline/day 1 visit, if the subject meets all eligibility criteria, they will subsequently be randomized to a

treatment regimen and enrolled. Subjects who meet screening visit eligibility but do not meet the baseline/day 1 visit eligibility criteria are considered screen failures. Screen failures may be eligible for rescreening up to 3 times, as described in Section 8.1.1.

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 the IRT system. 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.

5.5 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 3 times. Refer to Section 8.1.1.

6. Study Intervention

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

Note that **according to local regulations** in several countries, investigational product**(s)** are referred to as investigational medicinal product**(s)** and non-investigational product**(s)** **and other protocol-required therapies are referred to as non-investigational medicinal product(s)/auxiliary medicinal product(s)**.

6.1 Study Interventions Administered

6.1.1 Investigational Products

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

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

6.1.1.1 Dose Administration and Schedule

Efavaleukin alfa or placebo will be administered by SC injection Q2W starting on day 1. The following treatment groups are planned:

- efavaleukin alfa [redacted] 2W
- efavaleukin alfa [redacted] 2W
- efavaleukin alfa [redacted] Q2W
- placebo Q2W

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

The dose of investigational product must be given within ± 5 days of the scheduled time point (see Schedule of Activities Table 1-2 and Table 1-3). If that window is missed, that dose will not be administered, and the next dose will be administered at the next scheduled dosing date. Any 2 consecutive doses of investigational product must be at least 7 days apart.

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

Total volume of preparation, quantity administered, start date, start time, and box number of efavaleukin alfa/placebo are to be recorded on each subject's **electronic case report form (**eCRF**)**.

6.1.2 Medical Devices

No investigational medical devices will be used in this study.

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

Non-Amgen non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.1.3 Other Protocol-permitted Therapies

6.1.3.1 Immunosuppressants/Immunomodulators

Immunosuppressants/immunomodulator agents and doses should remain stable from ≥ 8 weeks prior to screening through week 52. Investigators may reduce dosage of immunomodulators and/or immunosuppressants if the subject develops unacceptable side effects or abnormal laboratory values attributable to these medications.

6.1.3.2 Oral Corticosteroids

Subjects who are taking OCS prior to screening should remain on a stable dose of OCS between ≥ 2 weeks prior to screening through week 12, with some exceptions as defined below. Initiation or temporary increases in the OCS dosage is not encouraged but are allowed if initiated at any time between day 1 and week 10 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 may begin tapering OCS after the week 12 assessment up to the week 44 assessment with initiation of tapering based upon clinical judgement of the treating physician. The tapering schedule should be directed at the discretion of the investigator but should generally not be tapered more than 20% of the prior dose per week. Tapering OCS before week 12 is not encouraged but may be allowed based upon investigator's judgement. Between weeks 44 and 52, the OCS dosing must again remain stable.

6.1.3.3 Topical Corticosteroids and Topical Calcineurin Inhibitors

Subjects who are using topical corticosteroids or topical calcineurin inhibitors should remain on a stable regimen during the study but may discontinue topical corticosteroids or calcineurin inhibitors at any time if clinically indicated.

6.1.3.4 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 a stable dose from day 1 through week 52. No initiation or increases in NSAIDs are allowed within 2 weeks of the week 52 visit. NSAIDs used for SLE disease activity should be held for 24 hours prior to scheduled visits. Subjects can return to their regular doses immediately after the clinical visit is complete. Discontinuation or reduction in frequency or dose of NSAIDs or other analgesic therapy dose during the study is allowed based on the investigator's judgment. Initiation or increases in NSAIDs or other analgesic therapy doses during the

study are allowed if: 1) subject is on baseline dose within 24 hours of scheduled efficacy assessments and 2) the subject returns to baseline dose within the subsequent 2 weeks of initiation or increase and 3) it is not within 2 weeks prior to the week 52 visit.

6.1.3.5 Anti-proteinuria Agents

Subjects with proteinuria due to SLE and taking anti-proteinuria agents (eg, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors), should remain on stable doses from day 1 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) during the study should be avoided.

6.1.4 Other Treatment Procedures

6.1.4.1 Home Health Care Visits

If permitted by local regulations, the investigator may utilize a qualified home health care service provider, approved by sponsor, for collection of PK and biomarker samples (investigational product will not be administered at these visits). In addition to PK and biomarker sample collection, safety assessments including 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 visits, all the information collected will be documented on the home health care services visit worksheet and provided 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.

6.1.5 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 and partners for whom Amgen

manufactures the material. This includes all components distributed with the drug such as packaging drug containers, delivery systems, labelling, and inserts.

This includes efavaleukin alfa/placebo provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product(s) (efavaleukin alfa/placebo), non-investigational products supplied by Amgen are to be reported.

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

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

- investigational therapies or commercially available biologic agents with immunosuppressive/immunomodulatory activity (eg, rituximab, abatacept, belimumab, or anifrolumab)
- cytotoxic agents including: chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents
- live vaccines
- T cell depleting agents (eg, antithymocyte globulin, Campath)
- IL-2 based therapies (eg, Proleukin)
- Intravenous, intra-articular, intramuscular, or intralesional corticosteroids, including adrenocorticotropic hormone
- intra-articular hyaluronic acid injections
- JAK inhibitors and TYK inhibitors
- immune checkpoint inhibitors

6.2 Dose Modification

6.2.1 Dose Treatment Group Study Escalation/De-escalation and Stopping Rules

All subjects will receive a fixed dose of the investigational product (efavaleukin alfa/placebo) according to the randomization assignment. No dose adjustments will be allowed.

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

6.2.2.1 Amgen Investigational Product: Efavaleukin Alfa

No dosage adjustments will be allowed.

The investigational product must be withheld if the following occur:

- any serious and/or clinically significant grade ≥ 3 adverse event deemed possibly related to investigational product until the adverse event resolves to $\leq$ grade 2.

Investigational product must be permanently discontinued if the following occur:

- any anaphylactic reactions or ≥ grade 3 acute allergic reactions deemed possibly related to investigational product by either the investigator and/or the sponsor that requires immediate treatment.
- any grade 4 life-threatening treatment-emergent adverse events deemed possibly related to investigational product.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study will be provide to the site.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects who meet all eligibility criteria will be randomized to receive efavaleukin alfa at [redacted] Q2W, [redacted] Q2W, [redacted] Q2W, or placebo Q2W in a double-blind manner. The randomization will be stratified by geographic region (North America + West Europe + Asia Pacific versus Rest of the World) and screening hSLEDAI score (≥ 10 versus < 10, with < 10 screening hSLEDAI capped at 80% of the study population). The randomization ratio starts as 1:1:1:1, and then may be adapted at planned IAs based on the clinical efficacy, as measured by SRI-4 response, based on RAR for the purpose of allocating more subjects to more efficacious doses and fewer subjects to less efficacious doses. The RAR will be implemented with a computerized system that assigns a treatment to subsequent subjects without unblinding any study personnel including the investigators or subjects.

The randomization will be performed via an IRT system. Each randomized subject will receive a single, unique randomization number via an IRT system at randomization. The randomization date is to be documented in the subject's medical record as registered in the IRT system and on the enrollment eCRF.

6.4.2 Blinding

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

6.4.2.1 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 study treatment 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.

6.4.2.2 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 except as specified (eg, Section 6.4.2.1).

6.5 Treatment Compliance

When subjects are dosed, they will receive investigational product directly from the investigator or designee, under medical supervision. The date and time of each dose administered will be recorded in the source documents and recorded in the eCRF.

6.6 Treatment of Overdose

The effects of overdose of this product are not known.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior therapies for SLE 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.

6.7.2 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 Sections 6.1.3 and 6.1.6.

Concomitant therapies (including vaccines) 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 6.1.3.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

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 Section 7.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies and/or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 1-2, Table 1-3, Table 1-4, and Section 8.1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies and/or procedures and subjects who require a dose of OCS for SLE above their baseline dose after week 16 and patients requiring either dose increases of the current immunosuppressants/new immunosuppressant/immunomodulator(s) should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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

- Decision by **s**ponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Pregnancy
- Disease flare

7.2 Subject Discontinuation/Withdrawal 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. Subjects who are withdrawn or removed from treatment or the study will not be replaced.

If a subject withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Table 1-3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 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

* Study discontinuation of 'decision by sponsor' will only be used in the event that the study is terminated, for any reason, including due to futility. Subjects who are still on study at the time of that decision may be terminated per sponsor decision.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if **they** repeatedly fail 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, they 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 should 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.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedules of Activities (see Table 1-2, Table 1-3, and Table 1-4).

If an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

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

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

Informed consent must be obtained before completing any screening procedure. After the subject has signed the informed consent form, the site will register the subject in the IRT system and screen the subject in order to assess eligibility for participation. The screening window is up to 33 calendar days.

All eligibility evaluations (conducted at the screening and baseline/day 1 visits prior to randomization) must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all

subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.5) as applicable. If a lab retest is required during screening, the sponsor should approve prior to being retested.

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

If a subject has not met all eligibility criteria at the end of the screening period and/or at the baseline/day 1 visit, the subject will be registered in IRT as a screen failure. Screen failures may be rescreened up to 3 times as follows:

- Subjects who do not meet the hSLEDAI criteria (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 will be required to wait at least 2 weeks prior to rescreening.
- Subjects who have not maintained stable immunosuppressant/immunomodulatory dosing will be required to wait at least 8 weeks prior to rescreening.
- Subjects who met eligibility criteria but were not able to enroll within the screening period (within the 33 days), can rescreen immediately.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 33 day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. All procedures noted in Section 8, including the informed consent and all laboratory parameters (Section 8.3.3) must be repeated with the following exception:

- Tuberculosis screening tests (QuantiFERON®-TB, T-spot test OR positive PPD), serologies for hepatitis B virus, hepatitis C virus and HIV do not need to be repeated, provided that rescreening occurs ≤ 12 months of screening visit and there is no patient's medical/epidemiological history suggestive of infection or recent exposure to cases of infection.

8.1.2 Treatment Period

Visits will occur per the Schedules of Activities (Table 1-2 and Table 1-3). 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.

If a subject discontinues investigational product prior to week 52, the subject will be encouraged to maintain the planned scheduled assessments through week 52 (Table 1-3). If the subject discontinues the study completely prior to week 52, the subject should complete an early termination (ET) visit (ie, week 52 visit procedures) which must be scheduled to allow for at least 6 weeks for safety data collection after last dose of investigational product.

8.1.3 Safety Follow-up Period

The safety follow-up period consists of a single safety follow-up visit which may be required at week 56 +5 days per the Schedule of Activities (Table 1-4). This visit only applies to subjects who require an additional visit following week 52 to ensure 6 weeks of safety data collection after last dose of investigational product (Section 8.1.2).

8.1.4 End of Study

Refer to Section 4.4 for End of Study definition.

All end of study procedures (ie, week 52/ET visit) should be performed at the final visit for subjects who discontinue study before week 52.

8.2 General Assessments

8.2.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

8.2.2 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.

8.2.3 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 eCRF. In addition to the

medical history above, SLE history must date back to the original diagnosis. The current severity will be collected for each condition that has not resolved.

8.2.4 Lupus Narrative

The screening lupus narrative form provides relevant information related to the subject's lupus. This form is to be used to provide a more holistic view of the subject's lupus history and current disease activity and aids in eligibility adjudication of the subject.

8.2.5 Physical Examination

Physical examinations will be performed as per the Schedules of Activities. Physical examination findings should be recorded on the appropriate eCRF (eg, medical history, Events).

8.2.6 Physical Measurements

Height in centimeters and weight in kilograms should be measured without shoes.

8.2.7 Substance Use 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.

8.2.8 Lupus Nephritis History

Obtain details regarding history of lupus nephritis as per Lupus Nephritis History Form.

8.2.9 Efficacy Assessments

Efficacy assessments are recommended to be performed prior to obtaining any blood samples and administration of investigational product. Assessments will be captured on a paper source then transcribed into the study database. It is highly recommended that the same assessor performs efficacy assessments at every timepoint for a given subject.

8.2.9.1 Hybrid Systemic Lupus Erythematosus Disease Activity Index

The hybrid SLEDAI (hSLEDAI) is a global index that evaluates disease activity and includes both laboratory and clinical parameters and consists of 24 items. The maximum score is 105. Hybrid SLEDAI is the index score used during the validation of the SLE Responder Index (SRI) (Navarra et al, 2011; Furie et al, 2011). The hSLEDAI includes scleritis and episcleritis in visual disturbance assessments. Scleritis and episcleritis should be confirmed by ophthalmologist and clinically stable if used for scoring purposes. Additionally, arthritis should be scored when > 2 joints manifest signs of inflammation strictly defined as the presence of tenderness plus **1** of the

following: swelling, effusion, warmth or erythema. The presence of tenderness alone is not sufficient and at least 3 joints, and not only 2, must be affected. In this study, for arthritis to be scored it is required to involve the small joints in the hands, wrists, or a combination of joints in the hands and wrists.

A total hSLEDAI $\geq$ 6 points is required for eligibility purposes, together with the presence of a clinical hSLEDAI $\geq$ 4 points. A clinical hSLEDAI score is a hSLEDAI score without the inclusion of points attributable to laboratory results including urine and immunologic parameters.

Findings should reflect activity during the 30 calendar days prior to the current visit.

8.2.9.2 British-Isles Lupus Assessment Group Index

The 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 (stable) or E (never present). The BILAG index can be converted into a numerical score (A grade = 12 points, B = 8, C = 1, D = 0, E = 0) (Yee et al, 2010). Findings should reflect activity during the 4-week period prior to the current visit and attributable to the subject's SLE.

8.2.9.3 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.

[redacted]

8.2.9.5 Swollen and Tender Joint Count

Swollen and tender joint counts will be performed as noted in the Schedule of Activities (Table 1-2 and Table 1-3).

The swollen and tender joint count assessments will be performed at the site by an experienced independent and blinded joint evaluator and must be identified on the delegation of authority for this responsibility. It is highly recommended that the same joint evaluator performs the assessments throughout the study for a given subject. The score for each joint will be recorded on a paper source then transcribed into the study database.

Joints that have been replaced are considered non-evaluable throughout the study.

Swollen Joint Count Assessments: A total of 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 separate 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.

8.2.9.6 Physician Global Assessment – Visual Analog Scale

The PGA is a visual analog scale (VAS) using 4 descriptive anchors for assessing disease activity over the last 4 weeks. When scoring the PGA VAS, 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 ≥ 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 and must be done before assessing the hSLEDAI and BILAG.

8.2.9.7 Physician Global Assessment – 4-Point Verbal Rating Scale

The PGA 4-Point Verbal Rating Scale uses 4 verbal descriptors for assessing the severity of disease since the last visit. The options for disease severity are none, mild, moderate, and severe.

This is a global assessment, factoring in all aspects of the subject's lupus disease activity. It should not reflect non-lupus medical conditions. This assessment will be completed by a health care provider and must be done before assessing the hSLEDAI and BILAG.

8.2.9.8 SRI-4

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 A score and no > 1 new BILAG B organ domain scores compared with baseline, AND < 0.3-points deterioration from baseline in PGA VAS score (scale 0 to 3).

[redacted]

8.2.9.10 Lupus Low disease Activity State (LLDAS)

The LLDAS will be calculated as detailed in Golder et al, 2019.

8.2.9.11 BILAG-based Combined Lupus Assessment (BICLA)

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; < 0.3-points deterioration from baseline in PGA VAS (scale 0 to 3); and no initiation of non-protocol treatment (Wallace et al, 2011; Wallace et al, 2014).

8.2.9.12 Patient Reported Outcomes

Patient reported outcomes should be completed prior to any assessments and before being clinically evaluated by the investigator or designee.

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

8.2.9.12.1 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.

8.2.9.12.2 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 traits (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, 20**20**). 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.

8.2.9.12.3 LupusQoL

The LupusQoL is the US version of the 34-item LupusQol originally developed in the United Kingdom (Jolly et al, 2010; McElhone et al, 2007). This is a SLE-specific

health-related quality of life instrument. 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.

8.2.9.12.4 Symptom Questionnaire

The Symptom Questionnaire is a new patient reported outcome instrument to evaluate inflammatory symptoms, non-inflammatory symptoms, and flare (Pisetsky et al, 2019). The items are based on a 11-point numerical rating scale, with 1 item being a choice of yes or no, all with a 7-day recall. Response to therapy and psychometric properties of the questionnaire will be evaluated with data derived from this study.

8.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedules of Activities see (Table 1-2, Table 1-3, and Table 1-4).

8.3.1 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 signs eCRF. The temperature location should be oral, forehead, 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 eCRF. Record all measurements on the vital signs eCRF.

8.3.2 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals. The investigator or designee will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

8.3.3 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1-2, Table 1-3, and Table 1-4) 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 Events eCRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject’s baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

Abnormal laboratory values that are considered to be clinically significant by the investigator must be repeated as soon as possible to rule out laboratory error. Persistent abnormal laboratory values should be followed-up until they return to normal or until an etiology of the persistent abnormality is determined.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 1-2, Table 1-3, and Table 1-4).

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

8.3.3.1 Serum Complement, Anti-dsDNA, and Anti-phospholipid Antibody Testing

All subjects will have samples for C3, C4, anti-dsDNA and anti-phospholipid antibody collected as outlined in the Schedule of Activities (Table 1-2 and Table 1-3).
Anti-dsDNA will be **done** for hSLEDAI determination throughout the study and will be collected as outlined in the Schedule of Activities (Table 1-2 and Table 1-3).

8.3.3.2 Tuberculosis Testing

All subjects must receive either a PPD, QuantiFERON®-TB, or T-Spot test at screening. A chest X-ray will be performed for subjects with a positive **TB** test (ie, positive PPD or positive or indeterminate QuantiFERON®-TB or T-spot test).

8.3.3.2.1 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.

8.3.3.2.2 QuantiFERON®-TB or T-Spot Testing

If a QuantiFERON®-TB test is performed for eligibility, the test will be performed centrally with test kits provided. If a T-spot test is performed for eligibility, the test will be performed locally with test kits procured locally.

8.3.3.3 HIV Antibodies, Hepatitis B, and Hepatitis C Testing

Hepatitis B surface antibody (HBsAb), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C (HCAb), and HIV antibodies (where permitted by local regulations) will be assessed at screening.

8.3.4 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

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

8.3.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE version 5 and is described in Section 11.4.

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 (efavaleukin alfa/placebo) through the EOS are reported using the Events eCRF.

8.3.4.1.2 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 6 weeks (+5 days) after the last dose of the investigational product/end of study/safety follow-up visit, whichever occurs later, are reported using the Events eCRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee immediately and no later than 24 hours of the investigator's awareness of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor immediately and no later than 24 hours of it being available.

Since the criteria in 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.

8.3.4.1.3 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 investigational product, then these serious adverse events will be reported to Amgen

immediately and no later than 24 hours following the investigator's awareness of the event.

Serious adverse events reported **after the end of the study** 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 if the subject ends the study.

8.3.4.2 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. In the event that a local reaction occurs at the site of the investigational product administration, the adverse event is to be reported in the Events eCRF as "injection site reaction" and the specific location and symptoms associated with the injection site reaction should also be provided. If there are multiple signs or symptoms at an injection site, each symptom of the event should be reported individually.

8.3.4.3 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 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen immediately and no later than 24 hours following awareness 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 Events eCRF.

8.3.4.4 Regulatory Reporting Requirements for Safety Information

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 a study treatment under clinical investigation are met.

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

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

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For studies in which the treatment assignment is blinded, 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.

Amgen will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report [ASR] in the European Union) for the Amgen Investigational Product. In order to ensure that consolidated safety information for the trial is provided, this single DSUR will also include appropriate information on any other investigational products used in the clinical trial, if applicable.

8.3.4.5 Safety Monitoring Plan

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

8.3.4.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and through 6 weeks after the last dose of protocol-required therapies.

If a pregnancy is reported, the investigator is to inform Amgen immediately and no later than 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. 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 11.5.

Pregnancy Testing

A high sensitivity serum pregnancy test should be completed at screening and a high sensitivity urine pregnancy test should be completed prior to randomization 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 11.5. Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing using a high sensitivity urine pregnancy test should be performed at monthly intervals during treatment with the investigational product and at the follow-up safety assessment.

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

8.4 Pharmacokinetic Assessments

All subjects randomized to efavaleukin alfa will have **PK** samples assessed.

Blood samples will be collected for measurement of serum concentrations of efavaleukin alfa as specified in the Schedule of Activities (Table 1-2 and Table 1-3).

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

8.5 Pharmacodynamic Assessments

Lymphocyte subsets: Blood samples will be collected for all subjects at the time points indicated in the Schedule of Activities (Table 1-2 and Table 1-3) [redacted]

[redacted]

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

8.6 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 efavaleukin alfa. Additional samples are not collected for this part of the study. For subjects who consent to these analyses, DNA may be extracted.

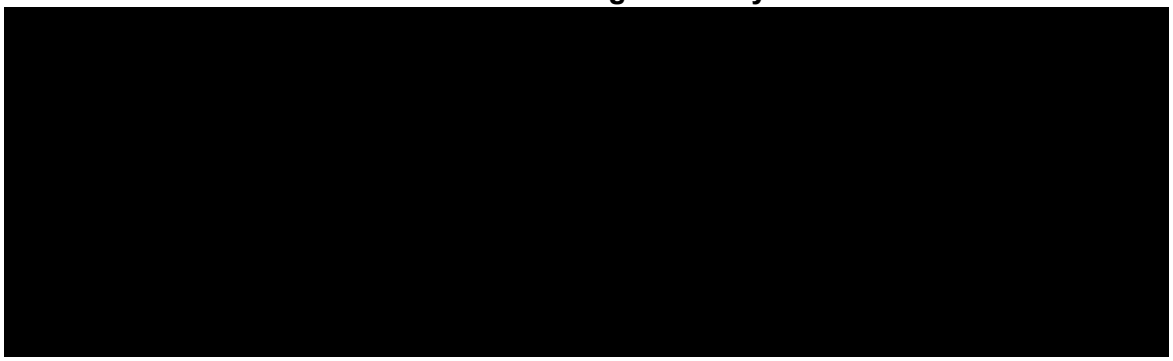
The final disposition of samples will be described in Section 11.6.

[redacted]

8.8 Biomarkers

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

8.8.1 Biomarker Assessment During the Study



8.8.2 Biomarker Development

Samples will also be collected **to develop or address biomarker hypotheses related to efavaleukin alfa activity**, eg, to evaluate potential biomarkers that may correlate with treatment response.

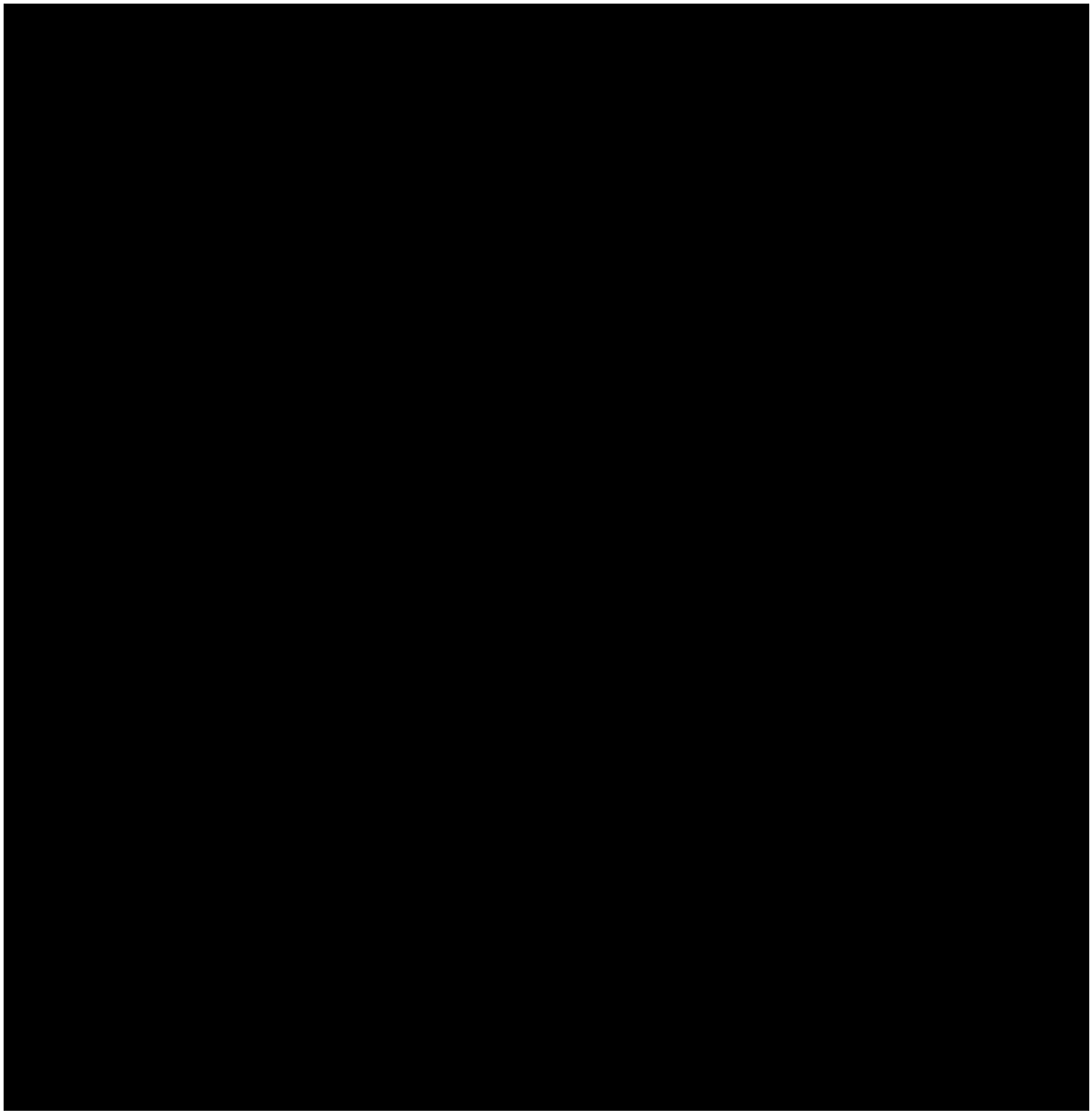
Blood will be collected for biomarker **development** at the time points specified in the Schedule of Activities (Table 1-2 and Table 1-3).

8.8.3 Biomarker Future Research

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

If consent is provided by subjects, any **remaining** samples collected per the Schedule of Activities, including samples **collected for biomarker assessments may** be **used** for future **research** as described in Appendix 6 (Section 11.6). No additional samples will be collected for future research.

Amgen or another third-party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to efavaleukin alfa to investigate and further understand inflammatory conditions.



[redacted]

9. Statistical Considerations

9.1 Statistical Hypotheses

At least 1 efavaleukin alfa dose will have greater efficacy than placebo as measured by the SRI-4 response rate at week 52 in subjects with active SLE with inadequate response to SOC therapy who are randomized, regardless of investigational product compliance; subjects using more than protocol-permitted therapies will be considered as nonresponders as specified in the primary estimand.

9.2 Sample Size Determination

The approximate sample size of 320 subjects is chosen to provide approximately 80% power to detect ≥ 25% absolute improvement for at least 1 efavaleukin alfa 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 once 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 subjects ensures if there is no interim signal for ET based on futility of all efavaleukin alfa doses, the trial will have adequate power to achieve the primary objective once all subjects have had the opportunity to complete the study.

9.2.1 Populations for Analysis

The following populations are defined:

Population	Description
Full Analysis Set	All subjects randomized in the study, with treatment assignment based on subjects' randomized treatment assignment.
Efficacy Analysis Set	All subjects randomized in the study. Data will be analysed based on subjects' randomized treatment assignment.
Safety Analysis Set	All randomized subjects who received at least 1 dose of investigational product. Data will be analysed according to actual treatment received.
PK Concentration Analysis Set	The PK Concentration Analysis 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 analysed according to the actual treatment received.
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 1 PK parameter adequately derived. PK parameter will be analysed according to the actual treatment received.

[redacted]

9.2.2 Covariates

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. The baseline covariates may include but are not limited to:

- Age, region, race, sex
- Baseline SLE disease activity
- Baseline OCS dose
- Baseline biomarkers

Stratification factors will be included as covariates in the model. If included as covariates in the model for treatment comparisons, the IRT value will be used to be consistent with the randomization scheme.

9.2.3 Subgroups

In addition to stratification factors, some covariates, not limited to those mentioned above, may be used for further exploration in subgroups. For subgroup analyses, the value collected from source-verified eCRF will be used to reflect the true clinical relevance of the covariate.

9.3 Statistical Analyses

The statistical analysis plan **(SAP)** will be developed and finalized before database lock for the final analysis. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 4.4.

9.3.1 Planned Analyses

9.3.1.1 Interim Analysis and Early Stopping Guidelines

Interim analyses will be conducted to allow for adaption of the randomization ratio for newly enrolled subjects to the 3 efavaleukin alfa 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 results of the IAs.
- The first IA will be executed after the first 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 the IAs to assess the likelihood of efavaleukin alfa treatment group being superior to placebo by a clinically meaningful difference.
  - From the second IA until before the last IA, if this likelihood is unacceptably low for all dose levels, the trial is recommended to stop for futility.
- At the 'all-subjects-week-24 IA', if this likelihood is sufficiently high with at least 1 efavaleukin alfa dose level, the IA triggers an administrative success signal. This would not alter ongoing or planned activities of this phase 2b study, but downstream planning for subsequent trials (eg, a phase 3 study) may commence. Analysis planned at each IA are listed in Table 1-1.

At IAs:

- From the second IA until 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% for all 3 efavaleukin alfa doses.
- 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 efavaleukin alfa dose, planning for a phase 3 study may be 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.

9.3.1.2 Final Analysis

[redacted]

9.3.2 Methods of Analyses

9.3.2.1 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, minimum, maximum, and number of subjects with observations. Safety endpoints will be summarized descriptively, including treatment-emergent adverse events and serious adverse events, clinically significant changes in laboratory values and vital signs, and incidence of antidrug antibodies.

9.3.2.2 Efficacy Analyses

Endpoint/Estimand	Statistical Analysis Methods
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 estimands. Details will be described in the SAP.
Exploratory	[redacted]

9.3.2.3 Safety Analyses

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

9.3.2.3.1 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, adverse events leading to discontinuation from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided.

9.3.2.3.2 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.

9.3.2.3.3 Vital Signs

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

9.3.2.3.4 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]

9.3.2.3.6 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.

9.3.2.3.7 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.

9.3.2.3.8 Exposure to Concomitant Medication

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

9.3.2.4 Other Analyses

Serum concentrations will be summarized descriptively by treatment for each PK sampling time point using PK Concentration Analysis Set. PK parameters (if deemed necessary) will be summarized with PK parameter analysis set. [redacted]. Medical history will be summarized by system organ class and preferred term and tabulated by treatment group and total using the Safety Analysis Set according to the actual treatment received.

10. References

Alcocer-Varela J, Alarcon Segovia D. Decreased production of and response to interleukin-2 by cultured lymphocytes from patients with systemic lupus erythematosus. *J Clin Invest*. 1982;69:1388-1392.

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.

Adams A, MacDermott EJ, Lehman TJA. Pharmacotherapy of lupus nephritis in children: a recommended treatment approach. *Drugs.* 2006;66(9):1191-1207.

Balsari A, Caruso A. Natural antibodies to IL-2. *Biotherapy*. 1997;10(1):25-28.

Bonelli M, Savitskaya A, Steiner CW, et al. Phenotypic and functional analysis of CD4+ CD25-Foxp3+ T cells in patients with systemic lupus erythematosus. *J Immunol.* 2009;182(3):1689-1695.

Boyman O, Sprent J. The role of interleukin.2 during homeostasis and activation of the immune system. *Nat Rev Immunol*. 2012;12:180-190.

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.

Castela E, Le Duff F, Butori C, et al. Effects of Low-Dose Recombinant Interleukin 2 to Promote T-Regulatory Cells in Alopecia Areata. *JAMA Dermatol*. 2014;150(7):748-751.

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;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;70(8):1256-1264.

Efavaleukin Alfa Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

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;63(12):3918-3930.

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.

He J, Zhang X, Wei Y, et al. Low-dose interleukin-2 treatment selectively modulates CD4(+) T cell subsets in patients with systemic lupus erythematosus. *Nat Med*. 2016;22:991-993.

He J, Zhang R, Shao M, et al. Efficacy and Safety of Low-Dose IL-2 in the Treatment of Systemic Lupus Erythematosus: A Randomised, Double-Blind, Placebo-Controlled Trial. *Ann Rheum Dis.* 2020;79(1):141-149.

Humrich J, von Spee-Mayer C, Siegert E, et al. Rapid induction of clinical remission by low-dose interleukin-2 in a patient with refractory SLE. *Ann Rheum Dis*. 2015;74:791-792.

Humrich J, von Spee-Mayer, Siegert E, et al. Low-dose IL-2 therapy in refractory SLE: results from single center phase I/IIa clinical trial **In: *2016 ACH/ARHP Annual Meeting*; 11-16 November 2016; Washington, DC. Abstract number 13L**.

Humrich JY, von Spee-Mayer C, Siegert E, et al. Low-dose interleukin-2 therapy in refractory systemic lupus erythematosus: an investigator-initiated, single-centre phase 1 and 2a clinical trial. *Lancet*. 2019;1(1):E44-E54.

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 **Rheumatol***. **2020 Jan;2(1):53-60.**

Khraishi M, Aslanov R, Dixit S, et . 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**. In: *2014 ACH/ARHP Annual Meeting*; 14-19 November 2014; Boston, MA. Abstract number 714**.

Koreth J, Matsuoka K, Kim HT, et al. Interleukin-2 and Regulatory T cells in Graft-versus-Host Disease. *N Engl J Med*. 2011;365:2055-2066.

Koreth J, Kim HT, Jones KT, et al. Efficacy, durability, and response predictors of low-dose interleukin-2 therapy for chronic graft-versus-host disease. *Blood*. 2016;128:130-137.

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.

Lieberman LA and Tsokos GC. The IL-2 defect in systemic lupus erythematosus disease has an expansive effect on host immunity. ***J Biomed Biotechnol*. 2010;2010:740619.**

Linker-Israeli M, Bakke AC, Kitridou RC, et al. Defective production of interleukin 1 and interleukin 2 in patients with systemic lupus erythematosus (SLE). *J Immunol*. 1983;130:2651-2655.

Long A, Cerosaletti K, Bollyky P, et al. Defects in IL-2R signaling contribute to diminished maintenance of FOXP3 expression in CD4+CD25+ regulatory T-Cells of type 1 diabetic subjects. *Diabetes*. 2010;59:407-415.

Long S, Rieck M, Sanda S, et al. Rapamycin/IL-2 combination therapy in patients with type 1 diabetes augments Tregs yet transiently impairs B-cell function. *Diabetes*. 2012;61:2340-2348.

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.

Malek TR and Castro I. Interleukin-2 receptor signaling: at the interface between tolerance and immunity. *Immunity*. 2010;33:153-165

Matsuoka K, Koreth J, Kim HT, et al. Low-dose interleukin-2 therapy restores regulatory T cell homeostasis in patients with chronic graft-versus-host disease. *Sci Transl Med*. 2013;5(179).

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.

Myara M, Amoura Z, Parizot C, et al. Global natural regulatory T cell depletion in active systemic lupus erythematosus. *J Immunol*. 2005;175:8392-8400.

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;377(9767):721-731.

Perol L, Lindner JM, Caudana P, et al. Loss of immune tolerance to IL-2 in type 1 diabetes. *Nat Commun.* 2016;6(7):13027.

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

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4(5):353-365.

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

Sadoun D, Rosenzwajg M, Jolly F, et al. Regulatory T-Cell Responses to Low-Dose Interleukin-2 in HCV-Induced Vasculitis. *N Engl J Med*. 2011;365:2067-2077.

Shao Q, Gao H. Progress in interleukin-2 therapy for rheumatic immune diseases by regulating the immune balance of T cells. *Scand J Immunol.* 2019;90(6):e12822.

Suen JL, Li HT, Jong YJ, Chiang BL, Yen JH. Altered homeostasis of $CD4^+$ $FoxP3^+$ regulatory T-cell subpopulations in systemic lupus erythematosus. *Immunology*. 2008;127:196-205.

Tchao N. AMG 592 is an investigational IL-2 mutein designed to induce highly selective expansion of regulatory T cells, the promise of interleukin-2 therapy. Presentation. Paris France, 2019.

van Steenbergen H, van Nies J, Ruyssen-Witrand A, et al. IL2RA is associated with persistence of rheumatoid arthritis. *Arthritis Research & Therapy*. 2015;17:244.

Golder V, Kandane-Rathnayake R, Huq M, et al. Lupus low disease activity state as a treatment endpoint for systemic lupus erythematosus: a prospective validation study. *Lancet Rheum*. 2019;1(2):e95-e102.

von Spee-Mayer C, Siegert E, Abdirama D et al. Low-dose interleukin-2 selectively corrects regulatory T cell defects in patients with systemic lupus erythematosus. *Ann Rheum Dis*. 2015;0:1-9.

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.

Watanabe M, Uchida K, Natagaki K, et al. Anti-cytokine autoantibodies are ubiquitous in healthy individual. *FEBS Lett.* 2007;581:2017-2021.

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.

Yee CS, Cresswell L, Farewell V, et al. Numerical scoring for the BILAG-2004 index. *Rheumatology*. 2010;49:1665-1669.

Yu A, Snowhite I, Vendrame F, et al. Selective IL-2 responsiveness of regulatory T cells through multiple intrinsic mechanisms supports the use of low-dose IL-2 therapy in type 1 diabetes. *Diabetes*. 2015;64:2172–2183.

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;77(3):355-363.

11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ACR	American College of Rheumatology
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Anti-CCP	**anti-cyclic citrullinated peptide**
Anti-dsDNA	anti-double stranded DNA
ASR	Annual Safety Report
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BICLA	BILAG based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
CD4+	**cluster of differentiation 4+**
CFR	US Code of Federal Regulations
CLASI	Cutaneous Lupus Erythematosus Area and Severity Index
Clinical hybrid SLEDAI	hybrid SLEDAI assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic parameters.
C_{max}	maximum observed concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
DMC	data monitoring committee
DSUR	Development Safety Update Report
ECG	electrocardiogram
eCRF	**e**lectronic **c**ase **r**eport **f**orm
EDC	electronic data capture
ET	early termination
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HIV	Human Immunodeficiency Virus
hSLEDAI	Hybrid Systemic Lupus Erythematosus Disease Activity Index
IA	interim analysis

Abbreviation	Explanation
IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL-2	Interleukin 2
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
JAK	Janus kinase
LLDAS	Lupus Low Disease Activity State
NCT	National Clinical Trials
NK	**natural killer**
NOAEL	no-observed-adverse-effect-level
NSAID	non-steroidal anti-inflammatory drugs
OCS	oral corticosteroids
PD	pharmacodynamic
PGA	Physician Global Assessment
[redacted]	
PK	pharmacokinetic
PPD	purified protein derivative
PROMIS	Patient-Reported Outcome Measurement Information System
PT	prothrombin time
Q2W	every 2 weeks
QLT	**quality tolerance limit parameter**
RA	rheumatoid arthritis
RAR	Response Adaptive Randomization
RBC	red blood cell
SAP	statistical analysis plan
SC	subcutaneous
[redacted]	
SF36v2	Medical Outcomes Short Form 36 version 2 questionnaire
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000

Abbreviation	Explanation
SLICC	Systemic Lupus International Collaborating Clinics
SOC	standard of care
SRI	Systemic Lupus Erythematosus Responder Index
TB	**tuberculosis**
TBL	total bilirubin
[redacted]	
Treg	regulatory T cells
TYK	Tyrosine kinase
TMF	trial master file
ULN	upper limit of normal
VAS	visual analog scale
[redacted]	

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the central laboratory and/or by the local laboratory. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

Table 11-1. Analyte Listing[a]

Central Laboratory: Chemistry	**Central Laboratory: Hematology**	**Other Labs**
Sodium	RBC	**Central Laboratory:**
Potassium	Hemoglobin	Hep B surface antigen
Chloride	Hematocrit	Hep B surface antibody
Bicarb	MCV	Hep B core antibody
Total protein	MCH	Hep C antibody
Albumin	MCHC	Antinuclear antibody
Calcium	RDW	Anti-dsDNA
Adjusted calcium	Reticulocytes	C3 and C4
Magnesium	Platelets	HIV antibody
Phosphorus	WBC	Lymphocyte subsets
Glucose	Differential	Serum pregnancy test
BUN or Urea	• Bands/stabs	PK samples[b]
Creatinine	• Eosinophils	PGx samples
Total bilirubin	• Basophils	Quanti**FERON®-**TB
Direct bilirubin	• Lymphocytes	Antiphospholipid Ab (lupus
ALP	• Monocytes	anticoagulant, anticardiolipin
LDH	• Total neutrophils	Ab [IgG and IgM], Anti-β2
AST (SGOT)	• Segmented neutrophils	glycoprotein1 Ab [IgG and
ALT (SGPT)		IgM])
GGT	**Central Laboratory: Urinalysis**	anti-Smith
Creatinine clearance by	Protein/creatinine ratio	anti-RNP
MDRD	Specific gravity	anti-SSA/Ro/anti-SSB/La
C-reactive protein	pH	Rheumatoid factor
CK	Blood	anti-CCP
	Protein	**Local Laboratory:**
Central Laboratory: Coagulation	Glucose	Urine Pregnancy
PT/INR	Bilirubin	PPD or T-spot
aPTT	WBC	FSH
	RBC	Coombs' test[c]
Central Laboratory: Thyroid Panel	Epithelial cells	
TSH	Bacteria	
free T4	Casts	
	Crystals	

Ab = antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; anti-CCP = anti-cyclic citrullinated peptide; anti-dsDNA = anti-double stranded DNA; anti-RNP = anti-ribonucleoprotein; anti-SSA/Ro = anti-Sjögren's-syndrome related antigen A; anti-SSB/La = anti-Sjögren's-syndrome related antigen B; aPPT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatinine kinase; FSH = follicle stimulating hormone; GGT = gamma glutamyl transferase; HDL = high density lipoprotein; Hep = hepatitis; HIV = Human Immunodeficiency Virus; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MDRD = Modification of Diet in Renal Disease; PD = pharmacodynamic; PGx = pharmacogenetics; PK = pharmacokinetic; **PPT = purified protein derivative;** PT = prothrombin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell count

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

[b.] 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.

[c.] Although Coombs' test is part of the BILAG 2004 disease activity index, this test is required only, when in the opinion of the investigator, there is a clinical justification to conduct direct Coombs' test. In such cases, the test needs to be performed. Sites will be reimbursed by Amgen for Coombs' tests and this will be reflected in sites' contracts.

If the subject is being followed for possible drug induced liver injury (DILI), the analytes included in Table 11-2 may be tested at the local laboratory depending on the clinical situation (see Section 11.7).

Table 11-2. DILI Potential Analyte Listing

Chemistry	Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, WBC Count, WBC Differential
Coagulation	PT, INR
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus NA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, Hepatitis B Virus DNA Genotyping, Hepatitis B Virus Surface Antibody, Hepatitis C Antibodies, Hepatitis C Virus RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, IgG, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

Independent Data Monitoring Committee

An Independent Biostatistics Group (IBG) will perform the interim analysis (IA) and provide the interim report to an independent unblinded Data Monitoring Committee (DMC). The first DMC meeting for safety will occur after first 20 subjects complete week 12 visit, and approximately every 12 weeks thereafter. 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, Investigator's Brochure, 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 protocol amendments and changes to the informed consent document that Amgen distributes to the site. 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 US 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 their 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 a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

If important new information becomes available that may be **relevant** to the **subject's** consent during their participation in the study**, subjects will be reconsented**.

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.

The 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 **c**ase **r**eport **f**orm (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.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, 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.

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the **s**ponsor's systems. The **s**ponsor uses access-controlled systems to house, review and analyze subject data.

These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The **s**ponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the **s**ponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

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.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be prepared in accordance with Amgen's publications policy and submitted to Amgen for review. 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, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All

persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or eCRF 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 eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered **o**n the eCRF.

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.

The sponsor or designee will perform ongoing source data verification to confirm that data entered **on** the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements 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 eCRFs, 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, eCRFs 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 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.

Quality tolerance limit parameters (QTLs) will be pre-defined in the QTL definitions table to identify possible systematic issues that can impact participant safety and/or reliability of the study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTL threshold limits for these parameters and remedial actions taken will be summarized in the clinical study report.

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

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

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

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom they have delegated study duties. All persons authorized to make entries and/or corrections on eCRFs 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 eCRF data are obtained. These include but are not limited to hospital records, clinical

and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and eCRF entries if the eCRF 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 or certain demographic information).

Data reported on the CRF or entered in the eCRF 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 **i**nvestigator 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.

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

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

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the **i**nvestigator 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 a separate 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.

11.4 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 study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse 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 study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events 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 Events case report form (CRF). • The investigator must assign the following mandatory adverse event attributes: – Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); – Dates of onset and resolution (if resolved); – Did the event start prior to first dose of investigational product; – Assessment of seriousness; – Severity (or toxicity defined below); – Assessment of relatedness to investigational product (efavaleukin alfa/placebo), other protocol-required therapies, devices, and/or study-**required** activity and/or procedures; – Action taken; and – Outcome of event. • 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 Events eCRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization in lieu of completion of the Events eCRF. • 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(s), protocol-required therapies, device(s), and/or study-**required** activity and/or procedure(s) and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that they have reviewed the adverse event/serious adverse event and has provided an assessment of causality. For sites reporting serious adverse events via electronic data capture (EDC), the investigator or sub-investigator must confirm causality in EDC within 72 hours of the serious adverse event being entered on the Events CRF. • 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. In this case, for sites reporting serious adverse events via EDC, the investigator or sub-investigator must reconfirm causality in the EDC system within 72 hours of the serious adverse event being entered on the Events CRF. • 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 postmortem findings including histopathology. • New or updated information will be recorded in the originally completed Events eCRF. • The investigator will submit any updated serious adverse event data to Amgen immediately and no later than 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 EDC system. • If the EDC system is unavailable, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event [eSAE] Contingency Report Form) (see Figure 11-1) immediately and no later than 24 hours of the investigator's awareness 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 system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1). • 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 11-1. Sample Electronic Serious Adverse Event Contingency Report Form

AMGEN
Study # 20200234
AMG 592

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax
The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

US: +888 814 8653

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 eeath. 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 theEvent may have been caused by IP or an Amgen device used to administer the IP?								**Outcome of Event** ·Resolved ·Not resolved ·Fatal ·Unknown	Check only if event is related to study procedure eg, biopsy
						AMG 592		<PIDevice>		<PIdevice>		<PIdevice>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	Yes✓		
				☐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

		Prior to, or at time of Event					**Action Taken with Product** 01 Still being Administered 02 Permanently discontinued 03 Withheld	**Lot # and Serial #**
IP/Amgen Device:		**Date of Initial Dose** Day Month Year	**Date of Dose** Day Month Year	**Dose**	**Route**	**Frequency**		
AMG 592	☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<IP/Device>	☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-056006 *Version 7.0 Effective Date: 1 February 2016*

Page 1 of 3

AMGEN Study # 20200234 AMG 592	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

<IP/Device>	☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test / Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20200234 AMG 592	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

Signature of Investigator or Designee -	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.*		

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

Study-specific contraception requirements for females of childbearing potential are outlined in Section 5.2. 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 6 weeks after the last dose of investigational product.

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 alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, 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 1 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 study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 6 weeks after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness 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 consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 6 weeks after the last dose of investigational product. 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 elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) 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 poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. 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 while pregnant (see Section 7.1 for details).

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

- In the event a male subject fathers a child during treatment, and for an additional 6 weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety immediately and no later than 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 consent 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 consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 6 weeks after the last dose of investigational product.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in **the** exclusion criteri**a (see Section 5.2)**.
- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 6 weeks after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

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: 20200234

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

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: 20200234

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

11.6 Appendix 6. Sample Storage and Destruction

When permitted by local regulations, any blood (eg, biomarker, PK) or skin-biopsy sample collected according to the Schedules of Activities (Table 1-2, Table 1-3, Table 1-4, Table 1-5, and Table 1-6) 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.

When permitted by local regulations and 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 efavaleukin alfa, characterize antibody response, 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 or skin 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 11.3 for subject confidentiality.

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

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

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

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

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

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin 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 11-3. 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 > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	> 3x ULN (when baseline was < ULN), in the presence of no important alternative causes for elevated AST/ALT and/or TBL values
	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 efavaleukin alfa is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-3) 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 immediately and no later than 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate **c**ase **r**eport **f**orm (CRF) (eg, Events eCRF) 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 11.4.

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 11-3 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, 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, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels

- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including 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 **PK** 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 eCRFs.

Amendment 4

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

Amgen Protocol Number Efavaleukin Alfa 20200234

EudraCT Number: 2020-003509-72

NCT Number: NCT04680637

Amendment Date: 06 March 2023

Rationale:

This protocol is being amended to remove the specific reference to anti-dsDNA assay (Phadia) in order to allow for regional difference in assay being performed. Additional updates to exclusion for active infection and general updates for clarity have been incorporated in various sections of the protocol which represent minor modifications, clarifications, and grammatical corrections. Updates to the protocol have been made to align with the most recent protocol template to ensure compliance with current regulatory requirements. The following changes have been implemented to:

- Include summaries for Benefit/Risk Assessment and Study Assessments and Procedures to the protocol Synopsis section, in accordance with European Union Clinical Trials Regulation (EU-CTR) (Section 1.1).
- [redacted]
- Update pregnancy test assessment to clarify that urine pregnancy test is to be performed prior to randomization (Section 1.3 [Table 1-2] and exclusion criterion no. 226)
- Remove specific reference to Phadia assay in order to allow for regional differences in the assay for anti-double stranded DNA (Section 1.3, Section 5.1 [criterion no. 103], and Section 8.3.3.1).

- Update exploratory endpoints (Section 3) to:
  - [redacted]
  - [redacted]
- Update inclusion criterion no. 103 to include anti-Smith test.
- Update exclusion criteria (Section 5.2) to:
  - Update exclusion criteria for active infection prior to screening (from 4 weeks to 2 weeks) (criterion no. 205).
  - Include “presence of anti-cyclic citrullinated peptide [anti-CCP] and rheumatoid factor OR current history of RA (rheumatoid arthritis) OR presence of erosive arthritis on imaging” as example of diagnosis of any chronic inflammatory disease other than systemic lupus erythematosus (criterion no. 232).
  - Include tyrosine kinase inhibitor as prohibited medication during the study (criterion no. 237).
  - Add a new criteria to state that female subjects of reproductive potential must agree not to donate eggs during the study and for 6 weeks after receiving the last dose of investigational product (new criterion no. 239).
- Refer to auxiliary medicinal product, in accordance with EU-CTR (Section 6).
- Clarify that samples testing positive for anti-efavaleukin antibodies will also be tested for neutralizing antibodies (Section 8.7).
- Include minor language updates in Biomarker Development and Future Research sections to align with current protocol template version 29.0, effective date 25 May 2022 (Section 8.8.2 and Section 8.8.3).
- Minor updates in the list of references (Section 10).
- Minor updates in the list of abbreviations (Section 11.1).
- Make administrative and editorial changes throughout the protocol for clarification.

Amendment 3

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

Amgen Protocol Number Efavaluekin alfa (AMG 592) 20200234

NCT04680637

Amendment Date: 21 October 2022

Rationale:

This protocol has been amended to:

- Add back the requirement for an independent blinded joint evaluator to conduct joint count assessments (number of tender and swollen joints). In the recently approved protocol amendment 2, this requirement was removed, and it needs to be re-incorporated to ensure consistency of the evaluation of this parameter in the trial.
- Incorporate administrative and editorial changes (including document version date, grammatical, typographical, abbreviations, and formatting) throughout the protocol.

Amendment 2

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

Amgen Protocol Number Efavaleukin Alfa 20200234

NCT04680637

Amendment Date: 01 September 2022

Rationale:

The main reason to conduct this protocol amendment is to remove 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. Important clarifications and grammatical corrections were also made. Based on this, the following changes were included:

- Efficacy Assessments:
    - Remove requirement for a separate blinded joint assessor (Section 8.2.9).
    - Clarify that the same assessor must perform efficacy assessments at every time point for a given subject (Sections 8.2.9 and 8.2.9.5).
    - Improve clarity of the definition of Systemic Lupus Erythematosus Responder Index (SRI-4) response and British Isles Lupus Assessment Group (BILAG)-based Combined Lupus Assessment (BICLA) response (Sections 8.2.9.8 and 8.2.9.11).

  - Clarify that for arthritis to be scored in this study, affected joints must involve small joints in hands, wrists, or a combination of joints in hands and wrists (Section 8.2.9.1).

- Endpoint for secondary objective aiming to evaluate efficacy of efavaleukin alfa 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 8.2.9.5 (Sections 1.1 and 3).
- New exploratory objective and endpoint were added to evaluate the efficacy of efavaleukin alfa on [redacted]
- Primary estimand language was revised to remove specific details as they are specified in the statistical analysis plan. The principles of how intercurrent events of protocol-prohibited rescue therapies are handled remains unchanged (ie, subjects will be considered as non-responders) (Sections 1.1 and 3)
- Table 1-3 Schedule of Activities – Treatment Period was updated to clarify that an early termination visit is required for all subjects who discontinue the study completely prior to week 52 (Table 1-3 and Section 8.1.4).
- Table 1-4 Schedule of Activities – Safety Follow-up/Week 56 Visit was updated to clarify that this table describes a separate safety follow-up visit which only applies to subjects who require an additional visit following completion of the entire planned 52-week treatment period to ensure at least 6 weeks follow-up data collection after last dose of investigational product (Table 1-4).
- [redacted]
- Statistical hypothesis was updated to align it with updates made to the primary estimand language (Sections 1.1 and 9.1).

- Human Exposure and Risk Assessment were updated to include data from completed and ongoing clinical studies that evaluate the safety profile of the investigational product including adverse drug reactions and potential risks (Sections 2.2.2.2. and 2.3).
- Clarify that at day 1, prior to randomization, the investigator must confirm disease activity and compliance and stability of Systemic Lupus Erythematosus (SLE) treatment (Sections 1.1 and 4.1).
- Justification for Investigational Product Dose was updated to include information regarding doses and recently collected data (Section 4.3).
- Information pertaining to eligibility assessment, which includes all the events that must occur before randomization and dosing, was re-organized to improve readability and clarity (Section 5).
- Update end of study definition for individual subjects to clarify that an individual subject is considered to have completed the study if they have remained on study for the entire treatment period and completed the safety follow-up, if applicable (Sections 4.4 and 8.1.4).
- Clarifications were provided on Safety Follow-up for subjects that complete the planned 52-week treatment period and for subjects that discontinue investigational product early to ensure safety follow-up is complete (Sections 1.1, 4.1, 4.4, 8.1.3, and Table 1-4).
- To ensure adequate safety surveillance for subjects who discontinue the study completely, instructions for scheduling the early termination visit were revised to state that this visit must be scheduled to allow for at least 6 weeks of safety follow-up after last dose of investigational product (Section 8.1.2).
- Interim analysis language was updated to remove details related to the administrative success 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 (Sections 1.1 and 9.3.1.1).

- 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. Additionally, it was clarified that the number of interim analyses will depend on the observed enrollment rate (Table 1-1).
- Add Biomarker Discovery section to describe collection of biomarker samples during the study, specify the type of sample to be collected, and include a description of the use of these samples (Sections 8.8.1, 8.8.2, 8.8.3, and 8.9.2).
    - To maintain consistency between the Schedule of Activities (Tables 1-2, 1-3, 1-5, and 1-6) and Biomarker Discovery section, the name of the Biomarker Assessment for sample collection was changed to Biomarker discovery.
- Inclusion criteria was updated to (Section 5.1):
    - Criterion 103: clarify that results of the Phadia method will be used for the purposes of Hybrid Systemic Lupus Erythematosus Disease Activity Index (hSLEDAI) scoring during screening and throughout the study and not for SLE classification criteria.
    - Criterion 110: clarifications on protocol specific rules for arthritis hSLEDAI and alopecia scoring.
    - New criterion (code 111): add affiliation to social security scheme as a requirement for France.
- Exclusion criteria was updated to (Section 5.2):
    - Criterion 205: clarify that current use, in addition to within 4 weeks prior to screening, of anti-infectives will also be considered as an exclusion criterion.
    - Criterion 214: revise washout period for Janus kinase (JAK) inhibitor by removing the 3-month window prior to screening requirement and retaining the less than 5 drug half-lives requirement (new code 237).

- Criterion 218: specify that prior or concomitant treatment with a biological agent must have immunosuppressive/immunomodulatory activity and provide additional examples of such treatment (new code 238). This update was also made to Excluded Treatments, Medical Devices, and/or Procedures During Study Period (Section 6.1.6).
- Criterion 231: clarify for lupus nephritis that current, in addition to within 1 year prior to screening, requirement of induction therapy will also be considered an exclusion criterion.
- Criterion 233: updated to clarify exclusion conditions for hepatitis B.
- Criterion 236: include Gilbert's Syndrome as an exception for presence of laboratory abnormalities during screening in serum total bilirubin.

- 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 5.5).
- Add intravenous corticosteroids, antifrolumab, and tyrosine kinase inhibitors to the list of excluded medications or treatments in the study (Section 6.1.6).
- Include a footnote in Analyte Listing table to provide the option for conduction of local lab testing if central lab testing is unavailable (Table 11-1 footnote a)
- For consistency, multiple sections of the protocol were updated to describe that individual who do not meet the criteria for participation in the study may be rescreened up to 3 times (Sections 1.1, 4.1, and 8.1.1).
- Clarify that lab retests required specifically during screening should be approved by the sponsor prior to conduction to avoid having delays of other study assessments that do not require sponsor pre-approval (Section 8.1.1).
- Remove instruction that subjects who screen fail within the screening period must wait until end of the screening period before being considered for rescreen (Section 8.1.1)

- Clarify that small joints in hands and wrists or a combination of joints in hands and wrists are required to score arthritis (Section 8.2.9.1).
- Provide specific instructions for capturing location and associated symptoms of reaction at the site of study drug administration (injection site reaction) as an adverse event (Section 8.3.4.2).
- For simplicity, Antibody Testing Procedures were updated to remove a redundant statement and to clarify that in the event of safety-related concerns more testing may be requested (Section 8.7).
- Incorporate updated language for safety collection and reporting of serious adverse events to align with current procedures (Table 1-2, Table 1-3, Table 1-4, Sections 6.1.5, 8.3.4, 8.3.4.1.2, 8.3.4.1.3, 8.3.4.3, 8.3.4.4, 8.3.4.6, Appendix 11-4, Appendix 11-5, and Appendix 11-7).
- Remove organ involvement as a baseline covariate on the treatment effect (Section 9.2.2).
- Incorporate an abbreviated study name, VIOLET, to have a short and concise name that can be used to refer to the study (Title page, Investigator's Agreement, Section 1.1).
- Administrative and editorial changes (including document version date, grammatical, typographical, abbreviations, and formatting) have been made throughout the protocol.

Amendment 1

Protocol Title: A Phase 2b Dose Ranging Study to Evaluate the Efficacy and Safety of Efavaleukin Alfa in Subjects with Active Systemic Lupus Erythematosus With Inadequate Response to Standard of Care Therapy

Amgen Protocol Number Efavaleukin Alfa 20200234

Amendment Date: 25 August 2021

Rationale:

The following changes were made to the protocol to incorporate regulatory authority recommendations and to clarify/correct other items in the protocol:

- The efficacy analysis set has been updated to include all subjects randomized in the study and not those who have received at least 1 dose of investigation product.
- To add the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria, lupus narrative and prior history of British Isles Lupus Assessment Group (BILAG) domains to the Schedule of Activities (SoA)
- To update BILAG reference and scoring.
- To add exploratory endpoint as below:

- Add blinded samples to protocol (lymphocyte subset)
- To add study adjudication language.
- To update the first data monitoring committee (DMC) meeting for safety to occur after the first 20 subjects complete the week 12 visit.
- Added a subsection to Section 2.3 (Risk Assessment) to include guidance to sites regarding coronavirus disease 2019 (COVID-19).
- Updated the following eligibility criteria:
  - #104 (now 110): changed upper limit of urine protein/creatinine ratio to 2000 mg/g
  - #201 (now 231): changed upper limit of urine protein creatinine ratio to 2000 mg/g and to exclude subjects with histological evidence of diffuse proliferative glomerulonephritis within 12 weeks prior to screening.

  - #203 (now 232): updated to indicate subjects with **chronic** inflammatory disease other than systemic lupus erythematosus (SLE) (eg, rheumatoid arthritis) are excluded; additionally, removed the use of "confirmed by investigator" and "based on investigator judgement"
  - #208 and #209 (now 233 and 234): removed reference to presence of viral DNA assessed by polymerase chain reaction (PCR) (Sections 1.3, 8.3.3.3, and 11.2 updated accordingly)
  - #211 (now 235): removed "per investigator judgement" and clarify that poorly controlled diabetes is hemoglobin A1C $>$ 7.
  - #217 and #230: minor clarification of wording
  - #222 (now 236): changed lower limit of glomerular filtration rate from 30 to 50 mL/min/1.73 m^2
- Sections 5.4, 5.5, and 8.1.1 updated to change numbering of rescreening attempts from 2 to 3.
- Section 6.2.2.1 updated to included guidance on which adverse events lead to withholding or permanently discontinuing efavaleukin alfa
- To update vital signs section of the protocol (Section 8.3.1) to include "forehead" as a temperature location.
- Section 7.2.1 updated to provide clarification for "decision by sponsor" as a reason to remove subject from study
- Section 8.3.3 updated to include guidance for the investigator to repeat any labs that are considered to be clinically significant to rule out laboratory error.
- Section 8.3.3.1 updated to remove the Phadia assay being used on anti-double stranded DNA (anti-dsDNA) to determine eligibility.
- Several sections of the protocol have been updated to include required alignments with current Amgen protocol template (Sections 6.1.6, 8.3.4.1.2, 8.3.4.1.3, 11.2, 11.3, and 11.4).
- Administrative and editorial changes (including grammatical, typographical, and formatting) have been made throughout the protocol.

Superseding Amendment

Protocol Title: A Phase 2b Dose Ranging Study to Evaluate the Efficacy and Safety of Efavaleukin Alfa in Subjects with Active Systemic Lupus Erythematosus With Inadequate Response to Standard of Care Therapy

Amgen Protocol Number AMG 592 20200234

Original Date:	09 October 2020
Superseding Original Date:	30 November 2020

Superseding Original Summary of Changes:

- Incorporate changes to align with the Data Monitoring Committee (DMC) Charter:
  - Clarify efficacy analyses language around interim analyses.
  - Change 'Futility' to 'Administrative Success' in Table 1-1.
  - Clarify efficacy assessment data will be captured on a paper source then transcribed or entered into the study database.
- Clarify language around primary estimand nonresponders.
- Remove unnecessary clarification around medication history.
- Clarify role of adjudication team. Central Review Team removed from protocol as routine data monitoring is not included in protocol.
- Clarify language around immunomodulator agents.
- Clarify timing of pharmacokinetic assessments.
- Clarify language around joint replacement.
- Clarify language around hepatitis B core antibody testing
- Added hepatitis B surface antibody to Table 11-1.
- Administrative, typographical, and formatting changes were made throughout the protocol.