Title Page

Protocol Title:		A Phase 2, Dose-finding, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis
Short Protocol Title:		Safety and Efficacy of Efavaleukin Alfa in Subjects with Moderately to Severely Active Ulcerative Colitis
Protocol Number:		20170104
Investigational Product:		Efavaleukin Alfa
Trade Name:		Not applicable
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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).

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Investigator's Agreement:

I have read the attached protocol entitled A Phase 2, Dose-finding, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis, dated **21 August 2024**, and agree to abide by all provisions set forth therein.

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

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

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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Title and Role of Investigator

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 2, Dose-finding, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Short Protocol Title: Safety and Efficacy of Efavaleukin Alfa in Subjects with Moderately to Severely Active Ulcerative Colitis

Study Phase: 2

Indication: Ulcerative colitis (UC)

Rationale

This phase 2 dose-finding study will assess the safety and efficacy of induction therapy with efavaleukin alfa in subjects with moderately to severely active UC. Efavaleukin alfa may be a viable treatment option for patients with moderately to severely active UC who have failed at least 1 of the following: conventional therapy (eg, immunomodulators, corticosteroids), biologic therapy, or targeted small molecule therapy (ie, Janus kinase [JAK] inhibitor).

Benefit/Risk Assessment

The safety of efavaleukin alfa has been evaluated in healthy subjects and in subjects with rheumatoid arthritis (RA), chronic graft versus host disease (cGvHD), and systemic lupus erythematosus (SLE). See Section 2.3 for more information on these studies. Efavaleukin alfa has been well tolerated in clinical studies and has an acceptable safety profile.

Based upon the totality of available safety data to date, the benefit/risk profile of efavaleukin alfa is favorable. The benefit risk assessment detailed in Section 2.3 supports the conduct of this phase 2 clinical trial in subjects with UC.

Reference should be made to the latest version of the Investigator's Brochure for further safety data on efavaleukin alfa.

Objective(s) and Endpoint(s)/Estimands

Objectives	Endpoints
Primary	
• To evaluate the effect of efavaleukin alfa on induction of clinical remission	• Clinical remission at week 12
Primary Estimand	
Variable: Clinical remission at week 12 Estimator: Difference in clinical remission rates Population: All subjects with moderately to severely active UC with inadequate response, loss of response, or intolerance to at least 1 of the following: conventional therapy, biologics, or targeted small molecules, who are randomized. Treatments: Each efavaleukin alfa dose group and placebo.	

Intercurrent event – composite variable strategy: Subjects will be considered as not meeting the endpoint if they meet any of the following criteria prior to the week 12 visit: • Initiation of or change in protocol-prohibited medication or concomitant UC medication • A colectomy (partial or total) or an ostomy • Discontinuation of investigational product	
Secondary	
• To evaluate the effect of efavaleukin alfa on induction of clinical response	• Clinical response at week 12
• To evaluate the effect of efavaleukin alfa on induction of endoscopic remission	• Endoscopic remission at week 12
• To evaluate the effect of efavaleukin alfa on induction of symptomatic remission	• Symptomatic remission at week 12
• To evaluate the effect of efavaleukin alfa as induction therapy on combined endoscopic and histologic remission	• Combined endoscopic remission and histologic remission of the colon tissue at week 12
• To evaluate the effect of efavaleukin alfa as induction therapy on change in histological score	• Change from baseline in histological score at week 12 as measured by Geboes score
• To evaluate the safety and tolerability of efavaleukin alfa	• Treatment-emergent adverse events

UC = ulcerative colitis

Overall Design

This phase 2 dose-finding study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week induction study of efavaleukin alfa in subjects with moderately to severely active UC who have failed at least 1 of the following: conventional therapy (eg, immunomodulators, corticosteroids), biologic therapy, or targeted small molecule. This study will be used to establish the efavaleukin alfa induction dose and maintenance dose/dosing regimens for continued development.

After completing all screening procedures and meeting eligibility criteria, subjects will be randomized in a 1:1:1:1 ratio to receive placebo or one of 3 efavaleukin alfa doses. Randomization will be stratified by prior experience with at least 1 biologic or targeted small molecule (yes/no) and corticosteroid use at randomization (yes/no).

Approximately 30% of enrolled subjects are allowed to be naïve to a biologic or targeted small molecule therapy. Screening may be closed for subjects naïve to biologic or targeted small molecule therapy, if based on current enrolled subjects and those in screening, it is anticipated that enrolment of subjects naïve to a biologic or targeted small molecule will be greater than 30% of the total planned enrolment. Subjects who

complete the 12-week induction period will have the option to continue treatment in an exploratory long-term treatment period if in the opinion of the investigator they may benefit from continued treatment. The long-term treatment period will explore the safety and efficacy of continued treatment with efavaleukin alfa for up to 40 weeks (total of up to 52 weeks of treatment). For a full list of study procedures, including the timing of each procedure, please refer to Section 8 and the Schedule of Activities (Section 1.3).

Interim analyses will be performed to assess futility (Section 9.4.1.1).

An independent Data Monitoring Committee (DMC) will oversee safety and overall conduct of the study (Section 11.3). The first 2 DMC meetings will occur after the first 20 subjects randomized have had the opportunity to complete the [redacted] and week 12 visits. Thereafter the DMC will plan to meet approximately every 3 months until Amgen is unblinded at the primary analysis. After Amgen is unblinded, the DMC will plan to meet every 6 months. Ad hoc meetings can be scheduled as needed. The DMC will also review all available safety and efficacy data for interim analyses (see Section 9.4.1.1 for timepoints).

Study Assessments and Procedures

Efficacy assessments include the modified Mayo score using centrally read endoscopies and mucosal biopsies at screening, week 12, and week 52 (or at early termination, as applicable), partial Mayo scores, biomarkers (fecal calprotectin, fecal lactoferrin, and high sensitivity C-reactive protein [hsCRP]), and patient reported outcomes (PROs). Safety assessments include physical examination, collection of adverse events and serious adverse events, chemistry, hematology, coagulation, urinalysis, pregnancy testing as applicable, and immunogenicity. This study also includes pharmacodynamic (PD) and pharmacokinetic (PK) assessments.

Number of Subjects

Approximately 240 subjects will be enrolled, 60 subjects per treatment group.

Summary of Subject Eligibility Criteria

The study will enroll men and women 18 to 80 years of age (19 to 80 in South Korea) with a diagnosis of UC for ≥ 3 months prior to enrollment. Subjects must have moderately to severely active UC defined by a modified Mayo score of 5 to 9, with a centrally read endoscopic subscore ≥ 2. Subjects must have experienced inadequate response or loss of response or intolerance to at least 1 conventional therapy or biologic or targeted small molecule therapy. Subjects must have stable doses of oral 5-aminosalicylates (ASA; stable dose for ≥ 2 weeks), oral corticosteroids (dose must be ≤ 20 mg/day prednisone or its equivalent and must have been stable for ≥ 2 weeks), budesonide (extended release tablets 9 mg/day; stable dose for ≥ 2 weeks), beclomethasone dipropionate (gastro-resistant prolonged-release tablet 5 mg/day; stable dose for ≥ 2 weeks), and conventional immunomodulators (azathioprine, 6-mercaptopurine, methotrexate; stable dose for ≥ 12 weeks). Exclusion criteria include a diagnosis of Crohn's disease or indeterminate colitis, UC limited to the rectum, clinical signs of fulminant colitis, toxic megacolon, or patients with a history of colectomy.

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 [redacted]

In the induction period, 4 dose groups are planned with a placebo group and 3 efavaleukin alfa dose groups: [redacted] µg [redacted] µg [redacted] and [redacted] µg [redacted]

In the long-term treatment period, subjects randomized to efavaleukin alfa during induction will remain on the same blinded dose throughout the long-term treatment period (both subjects who achieved clinical response at week 12 and those who did not achieve clinical response at week 12). Subjects randomized to placebo who achieved clinical response at week 12 will remain on placebo. Subjects randomized to placebo who did not achieve clinical response at week 12 will receive efavaleukin alfa [redacted] µg [redacted] in a blinded manner during the long-term treatment period.

For a full description of the investigational product doses, please refer to Section 6.1.1.

Statistical Considerations

The full analysis set will be used for analysis of the primary and secondary efficacy endpoints and will include all subjects randomized. The safety analysis set will include all randomized subjects who received at least 1 dose of investigational product.

Nominal p-values will be reported for the primary and secondary efficacy endpoints, with no adjustment for multiplicity.

The primary estimand will be analyzed using logistic regression to test the difference in clinical remission rates between efavaleukin alfa dose and placebo (Ge et al, 2011). The stratification factors as captured in the interactive response technology (IRT) will be included as covariates. The estimate of the risk difference between each efavaleukin alfa dose and placebo, the corresponding 2-sided 95% Wald confidence interval, and the p-value obtained from the logistic regression model will be provided. Missing primary endpoint data will be imputed using nonresponder imputation.

[redacted]

The primary analysis will occur when all subjects have had the opportunity to complete the week 12 visit. All primary and secondary objectives will be evaluated at the primary analysis.

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

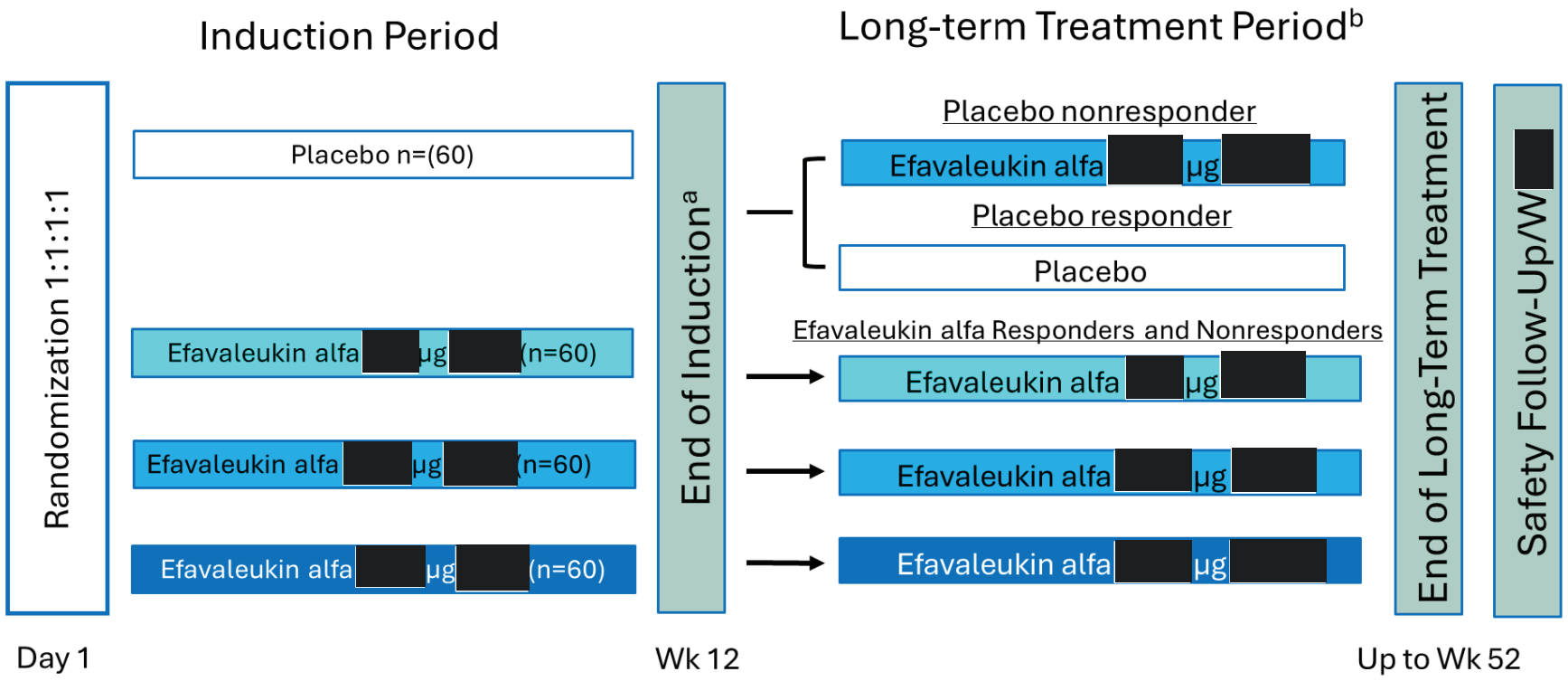
Statistical Hypotheses

The primary hypothesis is that at least 1 efavaleukin alfa dose will have greater efficacy compared to placebo as measured by clinical remission rates at week 12 in subjects with moderately to severely active UC.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



[redacted]

[a] Primary analysis for safety and efficacy. Assessment of clinical remission and clinical response using the modified Mayo Score in accordance with the Schedule of Activities (Table 1-1 and Table 1-2) and planned study objectives (Section 3).
[b] Eligible subjects will have the option to continue to be treated in an exploratory long-term treatment period for up to 40 additional weeks of treatment if in the opinion of the investigator they may benefit from continued treatment (total of up to 52-weeks of treatment).

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities – Screening and Start of Induction Treatment Period

	Screening		Randomization and Start of Induction Treatment Period				
DAY	**-35 to -1**	**-14 to -5**	**1**				**3 to 4**
			Pre-randomization	**Pre-dose**	**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			
Height	X						
Weight	X						
Medical History	X						
Substance Abuse History	X						
C-SSRS	X						
Vital Signs	X		X			X	X
ECG	X					X	X
Prior/ Onstudy UC Related Hospitalizations/Surgeries	X	→	→	→	→	→	→
Adverse Events					X →	→	→
Serious Adverse Events[a]	X	→	→	→	→	→	→
Prior/Concomitant Therapies Review	X	→	→	→	→	→	→
Randomization[b]				X			
LABORATORY ASSESSMENTS							
Pregnancy Test[c]	Serum		Urine				
FSH (postmenopausal women only)	X						
Tuberculosis Screening[d]	X						
HIV, Hepatitis B and C Screening[e]	X						
Hematology	X			X			
Chemistry	X			X			
Urinalysis	X			X			
Coagulation				X			
hsCRP				X			
C. difficile toxin and enteric pathogen testing	X						
Fecal Calprotectin[f]				X			
Fecal Lactoferrin[f]				X			
IMMUNOGENICITY ASSESSMENTS							
Anti-efavaleukin alfa antibody				X			

Footnotes defined on the last page of the table.

Table 1-1. Schedule of Activities – Screening and Start of Induction Treatment Period

DAY	Screening		Randomization and Start of Induction Treatment Period				
	-35 to -1	-14 to -5	1				3 to 4
			Pre-randomization	Pre-dose	Dose	6 to 24 hr postdose	48 to 96 hr postdose
BIOMARKER ASSESSMENTS							
Biomarker Development Sample				X		X	X
Lymphocyte Subset				X			
Biomarker Mucosal Biopsy Sample		X					
PHARMACOGENETIC ASSESSMENTS							
Pharmacogenetic Blood Sample[g]				X			
PHARMACOKINETIC ASSESSMENTS							
Pharmacokinetic Blood Sample				X		X	X
EFFICACY ASSESSMENTS							
Modified Mayo Score Review			X				
Partial Mayo Score Review		X		X			
Endoscopy		X[h]					
Mucosal Biopsy (histopathology)		X					
CLINICAL OUTCOME ASSESSMENTS							
Physician Global Assessment		X		X			
Mayo Daily Symptom Diary (daily)	X →						→
[redacted]							
IBDQ				X			
PGIS				X			
EQ-5D-5L				X			
STUDY TREATMENT							
Investigational Product Administration [redacted]	[redacted]						

C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L = EuroQol-5-Dimension 5 levels; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; IBDQ = inflammatory bowel disease questionnaire; PGIS = Patient Global Impression of Severity; UC = ulcerative colitis; [redacted]

[a] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.4.1.3 for additional details.

[b] Randomization will occur after confirmation of all eligibility criteria. The maximum time between initiation of screening and randomization is 35 calendar days. A subject must be in screening for at least 14 days prior to day 1 to enable a minimum of 7 days of Mayo daily symptom diary collection and receipt of results from the centrally read endoscopy.

[c] 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).

[d] Refer to Section 8.4.3.1.

[e] Refer to Section 8.4.3.2.
[f] Sites to provide the stool sample container for fecal calprotectin and fecal lactoferrin at the endoscopy visit; if the subject is eligible after endoscopy and scheduled for randomization, then the site can contact the subject to collect a stool sample the day before or morning of the Day 1 visit.
[g] DNA will be extracted only if subject provides additional consent for pharmacogenetics testing.
[h] Subjects who do not have a colonoscopy report available as source documentation at screening to confirm eligibility per inclusion criterion 105, will have a colonoscopy instead of rectosigmoidoscopy as the screening endoscopy for the study. Subjects with a combined stool frequency and rectal bleeding subscore ≥ 2 (using the average of the 3 most recent days in the 7 days prior to initiation of bowel preparation for the screening endoscopy) can proceed with endoscopy (Section 8.3.1.2).
[i] At visits on which investigational product is administered, all assessments must be completed in advance of investigational product administration unless otherwise noted. The dose of investigational product must be given within the window of time specified for the scheduled time point. If that window is missed, that dose will not be administered, and the next dose administered at the next scheduled dosing date. Any 2 consecutive doses of investigational product must be at least 7 days apart.

[redacted]

Table 1-2. Schedule of Activities – Induction Period

WEEK	Induction Treatment Period (Weeks)								W12
STUDY DAY ± VISIT WINDOW	[redacted] ± 5	[redacted] ± 1	[redacted] ± 5	[redacted] ± 5	[redacted] ± 5	[redacted] 6 to 24 hr post dose	[redacted] 48 to 96 hr post dose	[redacted] ± 5	85 ± 5
GENERAL AND SAFETY ASSESSMENTS									
Weight									X
Vital Signs	X	X	X	X	X			X	X
ECG[a]									X
Prior/ Onstudy UC Related Hospitalizations/Surgeries	←	—	—	—	—	—	—	—	→
Adverse Events	←	—	—	—	—	—	—	—	→
Serious Adverse Events[b]	←	—	—	—	—	—	—	—	→
Prior/Concomitant Therapies Review	←	—	—	—	—	—	—	—	→
LABORATORY ASSESSMENTS									
Pregnancy Test[c]			Urine		Urine				Urine
Hematology	X		X		X				X
Chemistry	X		X		X				X
Urinalysis			X		X				X
hsCRP			X		X				X
Fecal Calprotectin			X		X				X
Fecal Lactoferrin			X		X				X
IMMUNOGENICITY ASSESSMENTS									
Anti-efavaleukin alfa antibody	X		X		X				X
BIOMARKER ASSESSMENTS[a]									
Biomarker Development Sample	X	X		X	X	X	X		X
Lymphocyte Subset	X	X		X					X
Biomarker Mucosal Biopsy Sample									X
PHARMACOKINETIC ASSESSMENTS[a]									
Pharmacokinetic Blood Sample					X	X	X		X
EFFICACY ASSESSMENTS									
Modified Mayo Score Review									X
Partial Mayo Score Review	X	X	X	X	X			X	X
Endoscopy									X
Mucosal Biopsy (histopathology)									X

Footnotes defined on the last page of the table.

Table 1-2. Schedule of Activities – Induction Period

WEEK	Induction Treatment Period (Weeks) [redacted]								W12
STUDY DAY ± VISIT WINDOW	[redacted] ± 5	[redacted] ± 1	[redacted] ± 5	[redacted] ± 5	[redacted] ± 5	[redacted] 6 to 24 hr post dose	[redacted] 48 to 96 hr post dose	[redacted] ± 5	85 ± 5
CLINICAL OUTCOME ASSESSMENTS									
Physician Global Assessment	X	X	X	X	X			X	X
Mayo Daily Symptom Diary (daily)	←								→
[redacted]									
IBDQ			X		X				X
PGIS	X		X		X				X
PGIC			X		X				X
EQ-5D-5L			X		X				X
STUDY TREATMENT									
Investigational Product Administration[d]	[redacted]								
Investigational Product Administration – Long-term treatment									

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ECG = electrocardiogram; EQ-5D-5L = EuroQol-5-Dimension 5 levels; hsCRP = high sensitivity C-reactive protein; IBDQ = inflammatory bowel disease questionnaire; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; UC = ulcerative colitis; [redacted]

[a] If permitted by local regulations, the investigator may utilize a qualified home health care service provider, approved by sponsor, for collection of PK, biomarker samples, and ECG on visits without a scheduled administration of investigational product (See Section 6.1.4.1).

[b] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.4.1.3 for additional details.

[c] 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).

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

[redacted]

[f] Investigational product administration for subjects continuing in the long-term treatment will commence at the week 12 visit for the first dose (W12). For week 12 investigational product administration, the dosing window is up to + 3 days after the week 12 visit to allow for dosing on a separate day from the endoscopy. [redacted]

Table 1-3. Schedule of Activities – Exploratory Long-term Treatment Period

	Long-term Treatment Period																			
WEEK																				**W52/ ET[a]**
STUDY DAY ± VISIT WINDOW	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**365 ± 5**
GENERAL AND SAFETY ASSESSMENTS																				
Weight																				X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[b]						X						X						X		X
Prior/ Onstudy UC Related Hospitalizations/Surgeries	←																			→
Adverse Events	←																			→
Serious Adverse Events[c]	←																			→
Prior/Concomitant Therapies Review	←																			→
LABORATORY ASSESSMENTS																				
Pregnancy Test[d]		Urine		Urine		Urine		Urine		Urine		Urine		Urine		Urine		Urine		Urine
Hematology		X		X		X		X		X		X								X
Chemistry		X		X		X		X		X		X								X
Urinalysis		X		X		X		X		X		X								X
Fecal Calprotectin						X						X								X
IMMUNOGENICITY ASSESSMENTS																				
Anti-efavaleukin alfa antibody						X						X								X
BIOMARKER ASSESSMENTS[b g]																				
Biomarker Development Sample						X						X								X
Lymphocyte Subset						X						X								X
Biomarker Mucosal Biopsy Sample																				X
EFFICACY ASSESSMENTS																				
Partial Mayo Score Review		X		X		X		X		X		X		X		X		X		X
Endoscopy																				X[a]
Mucosal Biopsy (histopathology)																				X

Footnotes defined on the last page of the table.

Table 1-3. Schedule of Activities – Exploratory Long-term Treatment Period

	Long-term Treatment Period																			
WEEK	[redacted]																			**W52/ ET[a]**
STUDY DAY ± VISIT WINDOW	[redacted] ± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	365 ± 5
CLINICAL OUTCOME ASSESSMENTS																				
Physician Global Assessment		X		X		X		X		X		X		X		X		X		X
Mayo Daily Symptom Diary (daily)	←																			→
[redacted]																				
IBDQ																				X
PGIS																				X
PGIC																				X
EQ-5D-5L																				X
STUDY TREATMENT																				
Investigational Product Administration[e]	[redacted]																			

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ECG = electrocardiogram; ET = Early termination visit; EQ-5D-5L = EuroQol-5-Dimension 5 levels; hsCRP = high sensitivity C-reactive protein; IBDQ = inflammatory bowel disease questionnaire; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; UC = ulcerative colitis; [redacted]

[a] An ET is required for all subjects who discontinue the study completely prior to week 52. If a subject undergoes early termination soon after having their screening or week 12 endoscopy, the need for an ET endoscopy should be discussed with the Amgen physician.

[b] If permitted by local regulations, the investigator may utilize a qualified home health care service provider, approved by sponsor, for collection of PK, biomarker samples, and ECG on visits without a scheduled administration of investigational product (See Section 6.1.4.1).

[c] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.4.1.3 for additional details.

[d] 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).

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

[redacted]

[g] Blood samples must be collected prior to administration of investigational product.

Table 1-4. Schedule of Activities – Safety Follow-up

	Safety Follow-up[a]
Week	[redacted]
Study Day ± Visit Window	[redacted] **± 5 days**
GENERAL AND SAFETY ASSESSMENTS	
Vital Signs	X
UC Related Hospitalizations/Surgeries	X
Adverse Events	X
Serious Adverse Events[b]	X
Concomitant Therapies Review	X
LABORATORY ASSESSMENTS	
Pregnancy Test	Urine
Hematology	X
IMMUNOGENICITY ASSESSMENTS	
Anti-efavaleukin alfa antibody	X

UC = ulcerative colitis

[redacted]

[b] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.4.1.3 for additional details.

2. Introduction

2.1 Study Rationale

Regulatory T cells (Tregs) play a vital role in countering inflammatory processes in the gut and are integral to maintenance of mucosal homeostasis (Bollrath and Powrie, 2013). Efavaleukin alfa is an interleukin-2 (IL-2) mutein Fc fusion protein that has been developed to preferentially expand Tregs in patients with inflammatory diseases, including ulcerative colitis (UC). Support for the role of IL-2 in the treatment of UC comes from a recent clinical study of low dose IL-2, in which clinical response or remission was demonstrated in 9 of 15 subjects with moderate to severe UC after 8 weeks of treatment (Allegretti et al, 2020). Study 20170104 is a phase 2 dose-finding, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that will evaluate the safety and efficacy of efavaleukin alfa to induce remission in subjects with moderately to severely active UC who have experienced inadequate response, loss of response, or intolerance to at least 1 of the following: conventional therapy (eg, corticosteroids, immunomodulators), biologic, or targeted small molecule therapy (eg, Janus kinase [JAK] inhibitors). Subjects who complete the 12-week induction period will have the option to enter an exploratory long-term treatment period if in the opinion of the investigator they may benefit from continued treatment. The long-term treatment period will explore the safety and efficacy of continued treatment with efavaleukin alfa for up to 40 weeks (total of 52 weeks of treatment). Efavaleukin alfa may be a viable treatment option for patients with moderately to severely active UC who have failed at least 1of the following: conventional (eg, immunomodulators, corticosteroids), biologic, or targeted small molecule therapies. There is clear unmet medical need in this broad patient population (Section 5.1), which will be the patient population for this study.

2.2 Background

2.2.1 Disease

Ulcerative colitis is a chronic inflammatory bowel disease (IBD) with symptoms that include abdominal pain, bloody diarrhea, and fecal urgency, which can occur without warning, placing a significant burden on daily life. Ulcerative colitis most commonly affects adults 30 to 40 years of age, with approximately 20% of patients presenting before age 20 (Kelsen and Baldassano, 2008). The incidence and prevalence of UC have been increasing over time worldwide (Ungaro et al, 2017). The estimated United States incidence of UC is 9 to 12 cases per 100 000 persons per year, and the estimated prevalence is 205 to 240 cases per 100 000 persons (Danese and Fiocchi, 2011). The incidence of UC in Europe ranges from 0.9 to 24.3 per 100 000 person-years. The

highest incidence rates are observed in Scandinavia and the United Kingdom, while the lowest rates are seen in southern and Eastern Europe — suggesting a northwest/southeast gradient in IBD incidence (Burisch et al, 2013). The prevalence of UC in Europe varies from 2.4 to 294 cases per 100 000 persons. Extrapolating these numbers for the total European population indicates that there may be up to 2.1 million persons with UC in Europe (Burisch, et al, 2013). In patients with UC, there is an increased risk of colorectal cancer compared with the general population, with risk factors such as long duration of disease, extensive colonic involvement, severe inflammation and epithelial dysplasia, and childhood-onset disease. The goals of treatment in UC are to induce and maintain clinical response and endoscopic remission to prevent disability, colectomy, and colorectal cancer (Ungaro et al, 2017).

2.2.1.1 Limitations of Current Therapies

In patients with mild to moderate disease severity, conventional treatment typically consists of oral or topical aminosalicylates (5-ASAs) or topical steroids for induction of remission and oral and/or topical 5-ASAs for maintenance (Rubin et al 2019). 5-aminosalicyclic acid (5-ASA), a common first line therapy has been shown to be superior to placebo, yet a meta-analysis of 53 studies reported that 71% of the patients who initiated 5-ASA failed induction (Wang et al, 2016). In patients that are refractory to 5-ASA therapy or topical steroids, oral steroids can be used to induce remission (Rubin et al, 2019). However, steroids are not indicated for maintenance therapy in UC because of unwanted side effects to the extent that “corticosteroid-free remission” is a frequent treatment goal in clinical guidelines (Rubin et al, 2019; Ford et al, 2011).

Patients with moderate to severe disease are those who are dependent on or refractory to corticosteroids, have severe endoscopic disease activity (presence of ulcers), or are at high risk of colectomy. Advanced therapies for the treatment of moderately to severely active UC include immunosuppressants (eg, azathioprine and 6-mercaptopurine), biologic therapies such as anti-TNF inhibitors, anti-integrins (ie, vedolizumab), and interleukin-12 and -23 antagonists (ie, ustekinumab) as well as small molecule JAK inhibitors (eg, tofacitinib) (Danese et al, 2014). However, even with these therapies, a large percentage of patients are not able to achieve and/or maintain remission. A meta-analysis of 7 studies showed that 55% and 23% of subjects with UC who initiated an anti-TNF biologic responded and entered remission initially and that treatment response and remission were maintained in 39% and 24% of the subjects, respectively (Stidham et al, 2014). While these rates compared favorably to those for

placebo, they suggest that about half of the subjects failed to respond initially and that 61% of the initial responders lost their response over time. Similar data have been reported for vedolizumab; in a pivotal study of 374 subjects with UC, 47.1% and 16.9% achieved clinical response and clinical remission respectively at week 6 (Feagan et al, 2013). Finally, tofacitinib, an oral small molecule JAK inhibitor, presents as another option which compared favorable to placebo among patients with mild and moderate UC (Sandborn et al, 2017). In 2 identical pivotal trials of tofacitinib (OCTAVE 1 and 2), induction of remission at week 8 was achieved in 18.5% and 16.6% of patients treated with tofacitinib compared to 8.2% and 3.6% of patients treated with placebo (Sandborn et al, 2017).

Treatment options narrow significantly in patients with moderately to severely active UC who fail their first biologic therapy, which has been linked to a number of potential causes, including development of anti-drug antibody to anti-TNF biologic and vedolizumab (Mosli et al, 2015; Yarur et al, 2015). In the OCTAVE Induction 1 and 2 studies of tofacitinib, only 12% of the patients with prior anti-TNF biologic use entered remission at 8 weeks, compared with 23% in anti-TNF biologic naïve patients (Sandborn et al, 2017).

Other limitations of available UC agents include the time required for response (eg, anti-integrins can take up to 6 months for maximum benefit to be seen) (Tripathi and Feuerstein, 2019).

While treatment options are available for UC, there continues to be unmet need for new therapies with better safety and efficacy, particularly for achieving long term, steroid-free, remission and combined endoscopic and histologic remission.

2.2.1.2 Regulatory T Cells and Interleukin-2

Regulatory T cells are a subset of CD4+ T cells that suppress inflammation. Interleukin-2, a multi-functional cytokine produced predominantly by activated CD4+ T cells, is a key growth factor for Tregs and is essential for Treg maintenance, survival, and metabolism (Boyman and Sprent, 2012; Malek and Castro, 2010). A loss of homeostatic balance between Treg and other lymphocytes is considered a causative factor in many inflammatory conditions. In recent clinical studies, increasing Tregs with low dose recombinant IL-2 (Proleukin® [aldesleukin]) has yielded promising results in patients with inflammatory diseases, including chronic graft versus host disease (cGvHD), systemic lupus erythematosus (SLE), hepatitis C virus vasculitis, and UC

(Allegretti et al, 2020; Rosenzwajg et al, 2019; Koreth et al, 2016; Humrich et al, 2015; Matsuoka et al, 2013; Koreth et al, 2011; Saadoun et al, 2011).

Regulatory T cells play a vital role in countering inflammatory processes in the gut and are integral to maintenance of mucosal homeostasis (Bollrath and Powrie, 2013). Ulcerative colitis is associated with genetic polymorphisms in the IL-2 gene as well as the IL-10 gene, a suppressive cytokine produced by Tregs (Amgen internal data; Anderson et al, 2011; Festen et al, 2009). An open-label, single group, phase 1b/2a study of daily SC administration of low dose IL-2 was recently performed in subjects with moderate-to-severely active UC (Allegretti et al, 2020). Three sequentially increasing dose levels were tested (dose A: $0.3x10^6$ IU/m^2/day, dose B: $1x10^6$ IU/m^2/day, or dose C: $1.5x10^6$ IU/m^2/day) and Treg expansion was observed in all dosing cohorts, but Tcon activation was observed at the highest dose. Overall, 41.6% (10/24) of subjects achieved either clinical response or remission, after 8 weeks of treatment, as assessed by Mayo score, including 60% (9/15) of subjects in the dose B cohort alone. Low dose IL-2 was generally well tolerated; the most frequently reported adverse events included injection site reactions and malaise (Allegretti et al, 2020). These data provided preliminary evidence that expansion of Tregs using low dose IL-2 may ameliorate disease in UC patients.

2.2.2 Amgen Investigational Product Background: Efavaleukin Alfa

Efavaleukin alfa is an IL-2 mutein Fc fusion protein that has been developed to preferentially expand Tregs in patients with inflammatory diseases. Preclinical in vitro and in vivo studies have demonstrated that efavaleukin alfa exhibits greater selectivity for inducing Treg expansion over the expansion of other T cells and natural killer cells, relative to low dose recombinant IL-2 (refer to efavaleukin alfa Investigator's Brochure for more details). This greater selectivity of efavaleukin alfa may provide for greater efficacy and a wider therapeutic margin in inflammatory diseases relative to low dose recombinant IL-2 based modalities and, therefore, supports the investigation of efavaleukin alfa for the treatment of UC.

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

2.3 Benefit/Risk Assessment

Treatment of moderately to severely active UC has evolved in recent years. Progress has been made with the introduction of several new drug classes, including the anti-integrin vedolizumab, the interleukin-12 and -23 antagonist ustekinumab, and the

JAK-inhibitor tofacitinib, which have led to a significant improvement in response and remission rates (Danese et al, 2014).

Ulcerative colitis is characterized by a recurring pattern of remission and relapse that can progress to extensive inflammation of the colon, resulting in significant morbidity. Approximately one-third (31%) of patients with limited UC at diagnosis will have disease extension by 10 years (Roda et al, 2017). The 5-year and 10-year cumulative risk of colectomy is 10% to 15% (Fumery et al, 2018). The goal of treatment for moderately to severely active UC is to achieve resolution of rectal bleeding, normalization of bowel habits, and mucosal healing in order to delay UC-associated complications such as colectomy and colon cancer, and to maintain an acceptable health related quality of life (Ungaro et al, 2017). Investigational agents that utilize both novel targets and mechanisms of action, especially those that have shown clinical activity in first in human studies, have the potential to achieve these goals, particularly in patients with a high unmet need after their disease has progressed following treatment with available standard-of-care therapies.

Regulatory T cells play a vital role in countering inflammatory processes in the gut and are integral to maintenance of mucosal homeostasis (Bollrath and Powrie, 2013). With its novel mechanism of action, efavaleukin alfa is being developed for the treatment of UC, as it: a) exhibits greater selectivity for inducing Treg expansion over the expansion of other T cells and NK cells, relative to low dose recombinant IL-2, b) may provide greater efficacy and a wider therapeutic margin in inflammatory diseases relative to low dose recombinant IL-2-based modalities, c) offers less frequent dosing and greater convenience compared with low dose IL-2 and d) may have an improved safety and tolerability profile over existing UC therapies. In addition, clinical experience with low dose IL-2 in subjects with UC has provided proof of concept support for this approach.

The safety of efavaleukin alfa has been evaluated in healthy subjects and Phase 1 studies of subjects with rheumatoid arthritis (RA), cGvHD and SLE. Cumulative data from completed and ongoing Phase 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] μg [redacted] have been evaluated in subjects with RA over the course of a 12-week period (28 subjects). Repeated doses of up to [redacted] μg [redacted] have been evaluated in subjects with cGVHD over a 52-week period (32 subjects). Repeated doses of up to

[redacted] µg [redacted] have been evaluated in subjects with SLE over a 12-week treatment period (25 subjects).

Based upon the totality of available safety data through 26 April 2022, 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 these clinical studies include erythema, pruritus, exacerbation in subjects with RA, hypersensitivity, and injection site reaction. Potential risks include cardiovascular, respiratory, hematopoietic, changes in leukocyte population, immunomodulation, immunogenicity, and cytokine release syndrome. More information about the safety profile of efavaleukin alfa may be found in the latest version of the Investigator's Brochure.

The above benefit risk assessment supports the conduct of this phase 2 clinical trial in subjects with UC.

2.3.1 COVID-19

Amgen closely monitors the Corona virus-19 (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 patients and avoid undue burden on healthcare facilities.

Patients 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 224 and Section 6.1.6.

3. Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To evaluate the effect of efavaleukin alfa on induction of clinical remission	• Clinical remission at week 12
Primary Estimand	
Variable: Clinical remission at week 12 Estimator: Difference in clinical remission rates Population: All subjects with moderately to severely active UC with inadequate response, loss of response, or intolerance to at least 1 of the following: conventional therapy, biologics, or targeted small molecules, who are randomized. Treatments: Each efavaleukin alfa dose group and placebo. Intercurrent event – composite variable strategy: Subjects will be considered as not meeting the endpoint if they meet any of the following criteria prior to the week 12 visit: • Initiation of or change in protocol-prohibited medication or concomitant UC medication • A colectomy (partial or total) or an ostomy • Discontinuation of investigational product	
Secondary	
• To evaluate the effect of efavaleukin alfa on induction of clinical response	• Clinical response at week 12
• To evaluate the effect of efavaleukin alfa on induction of endoscopic remission	• Endoscopic remission at week 12
• To evaluate the effect of efavaleukin alfa on induction of symptomatic remission	• Symptomatic remission at week 12
• To evaluate the effect of efavaleukin alfa as induction therapy on combined endoscopic and histologic remission	• Combined endoscopic remission and histologic remission of the colon tissue at week 12
• To evaluate the effect of efavaleukin alfa as induction therapy on change in histological score	• Change from baseline in histological score at week 12 as measured by Geboes score
• To evaluate the safety and tolerability of efavaleukin alfa	• Treatment-emergent adverse events

UC = ulcerative colitis

Endpoint Definitions

• Clinical Remission	• Modified Mayo score 0 to 2 including rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopy subscore of 0 or 1 (modified so that 1 does not include friability)
• Clinical Response	• A decrease from baseline in the modified Mayo score of $\geq$ 2 points and at least 30% reduction from baseline, and a decrease in the rectal bleeding subscore of $\geq$ 1 or an absolute rectal bleeding subscore of 0 or 1
• Endoscopic remission	• Mayo endoscopy subscore of 0 or 1(modified so that a score of 1 does not include friability)
• Symptomatic remission	• Mayo stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0
• Combined endoscopic and histologic remission	• Combined endoscopic remission (Mayo endoscopy subscore of 0 or 1) and histologic remission of the colon tissue (Geboes Score $<$ 2.0; no neutrophils in the epithelium crypts or lamina propria and no increase in eosinophils, no crypt destruction and no erosions, ulcerations or granulation tissue)
• Safety and tolerability	• Subject incidence of treatment-emergent adverse events (including treatment-emergent adverse events for clinically significant changes in laboratory parameters and vital signs)

Phase 2 Induction Period

Exploratory	
• To explore the effect of efavaleukin alfa as induction therapy on total Mayo score, partial Mayo score and individual subscores	• Change from baseline in total Mayo score at week 12 • Change from baseline in partial Mayo score at each assessment through week 12 • Change in individual Mayo subscore at each assessment through week 12
• To explore the effect of efavaleukin alfa on induction of symptomatic and endoscopic remission without concomitant corticosteroid use	• Symptomatic remission at week 12 without concomitant corticosteroid use from baseline through week 12 • Endoscopic remission at week 12 without concomitant corticosteroid use from baseline through week 12

• To explore the effect of efavaleukin alfa as induction therapy on calprotectin levels in fecal samples	• Change from baseline in fecal calprotectin at week 12
• To explore the effect of efavaleukin alfa as induction therapy on lactoferrin levels in fecal samples	• Change from baseline in fecal lactoferrin at week 12
• To explore the effect of efavaleukin alfa as induction therapy on CRP levels	• Change from baseline in CRP levels through week 12
• To explore the immunological effects (pharmacodynamics) of efavaleukin alfa	• Fold changes from baseline of Treg, CD4+Tcon, CD8+ T cells, and NK absolute cell counts (cells/μL) after efavaleukin alfa administration
• To characterize the PK of efavaleukin alfa	• Trough and sparse postdose serum concentrations of efavaleukin alfa
• To explore efavaleukin alfa immunogenicity	• Anti-efavaleukin alfa antibodies and crossreactivity with IL-2 • Anti-efavaleukin alfa and anti-IL-2 neutralizing antibodies
[redacted]	
• To explore the effect of efavaleukin alfa as induction therapy on functioning and	• Change from baseline in social function and emotional function scores as measured by IBDQ at

health-related quality of life	week 12 • Changes from baseline in IBDQ overall score at week 12
• To explore the effect of efavaleukin alfa as induction therapy on changes in quality of life	• Change from baseline in VAS scores as measured by the EQ-5D-5L at week 12
• To explore the effect of efavaleukin alfa as induction therapy on UC-related hospitalizations	• Incidence and duration of UC-related hospitalizations at week 12
• To explore the effect of efavaleukin alfa as induction therapy on colectomy or UC-related complications	• Colectomy for UC or UC-related complications at week 12

CRP = C-reactive protein; EQ-5D-5L = EuroQol-5-Dimension 5 levels; IBDQ = Inflammatory Bowel Disease Questionnaire; IL-2 = interleukin-2; NK = natural killer; PK = pharmacokinetics; [redacted] UC = ulcerative colitis; [redacted]; VAS = visual analogue scale

Long-term Treatment Period

Exploratory	
• To explore the efficacy of long-term treatment with efavaleukin alfa	• Sustained clinical remission at week 12 and week 52 • Clinical remission at week 52 • Clinical response at week 52 • Endoscopic remission at week 52 • Corticosteroid-free clinical remission at week 52 in subjects receiving corticosteroids at randomization • Combined endoscopic and histologic remission at week 52
• To explore the long-term safety of efavaleukin alfa	• Treatment-emergent adverse events
• To explore efavaleukin alfa immunogenicity during long-term treatment	• Anti-efavaleukin alfa antibodies and crossreactivity with IL-2 • Anti-efavaleukin alfa and anti-IL-2 neutralizing antibodies
• To explore the effect of efavaleukin alfa long-term treatment on total Mayo score, partial Mayo score and individual subscores	• Change from baseline in total Mayo score at week 52 • Change from baseline in partial Mayo score at each assessment through week 52 • Change from baseline in individual Mayo subscore at each

	assessment through week 52
• To explore effect of efavaleukin alfa long-term treatment on calprotectin levels in fecal samples	• Change from baseline in fecal calprotectin at week 52
[redacted]	
• To explore the effect of efavaleukin alfa long-term treatment on functioning and health-related quality of life	• Change from baseline in social function and emotional function scores as measured by the IBDQ at week 52 • Change from baseline in IBDQ overall score at week 52
• To explore the effect of efavaleukin alfa long-term treatment on changes in quality of life	• Change from baseline in VAS scores as measured by the EQ-5D-5L at week 52

EQ-5D-5L = EuroQol-5-Dimension 5 levels; IBDQ = Inflammatory Bowel Disease Questionnaire; IL-2 = interleukin-2; [redacted]; UC = ulcerative colitis; [redacted]; VAS = visual analogue scale.

4. Study Design

4.1 Overall Design

This phase 2 dose-finding study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week induction study of efavaleukin alfa in subjects with moderately to severely active UC who have failed at least 1 of the following: conventional therapy (eg, immunomodulators, corticosteroids), biologic therapy, or targeted small molecule (eg, JAK inhibitors). This study will be used to

establish the efavaleukin alfa induction dose and maintenance dose/dosing regimens for continued development. Subjects who complete the 12-week induction period will have the option to be treated in an exploratory long-term treatment period for up to 40 additional weeks if in the opinion of the investigator they may benefit from continued treatment. The primary analysis will occur after all subjects have completed the week 12 visit or have early terminated. All primary and secondary objectives will be evaluated at the primary analysis. The objectives and endpoints for the study are defined in Section 3. The overall study design is described by a study schema in Section 1.2 (Figure 1-1).

4.1.1 Induction Period

Approximately 240 subjects will be assigned in a 1:1:1:1 ratio to placebo or 1 of 3 efavaleukin alfa dose parallel groups (n = 60 per group) as follows:

- Placebo [redacted]
- [redacted] µg [redacted]
- [redacted] µg [redacted]
- [redacted] µg [redacted]

Randomization will be stratified by prior experience with at least 1 biologic or targeted small molecule (yes/no) and corticosteroid use at randomization (yes/no). Approximately 30% of enrolled subjects are allowed to be naïve to biologic or targeted small molecule therapy. Screening may be closed for subjects naïve to biologic or targeted small molecule therapy, if based on current enrolled subjects and those in screening, it is anticipated that enrolment of subjects naïve to a biologic or targeted small molecule will be greater than 30% of the total planned enrolment. Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 9.2.

Clinical remission and clinical response will be assessed at the end of the 12-week induction period by the modified Mayo score using centrally read endoscopy subscore (see Section 8.3.1). Week 12 was selected as the time point for induction efficacy assessments based on available clinical data from a study of UC patients with low-dose IL-2 (Section 2.1). For efavaleukin alfa, 12 weeks is predicted to allow sufficient duration of therapy with sustained Treg expansion to provide an optimal induction remission rate. Once a subject completes safety and efficacy assessments at week 12, they will have an option to be treated in an exploratory long-term treatment period, if in the opinion of the investigator, they would benefit from continued treatment (Section 4.1.2).

If a subject discontinues investigational product during the induction period, 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 [redacted] If a subject undergoes ET soon after having their screening or week 12 endoscopy, the need for an ET endoscopy should be discussed with the Amgen physician.

Interim analyses will be performed to assess futility (Section 9.4.1.1).

An independent Data Monitoring Committee (DMC) will oversee safety and overall conduct of the study (Section 11.3). The first 2 DMC meetings will occur after the first 20 subjects randomized have had the opportunity to complete the [redacted] and week 12 visits. Thereafter the DMC will plan to meet approximately every 3 months until Amgen is unblinded at the primary analysis. After Amgen is unblinded, the DMC will plan to meet every 6 months. Ad hoc meetings can be scheduled as needed. The DMC will also review all available safety and efficacy data for interim analyses (see Section 9.4.1.1 for timepoints).

4.1.2 Long-term Treatment Period

Subjects who complete the safety and efficacy evaluations at week 12, have not discontinued investigational product, and who in the opinion of the investigator may benefit from continued treatment, will have the option to continue treatment in an exploratory long-term treatment period. The long-term treatment period will provide opportunity to explore the long-term safety and efficacy of continued treatment with efavaleukin alfa for up to 40 weeks (total of up to 52 weeks of treatment). During the long-term treatment period, subjects will continue to receive their assigned blinded dose of investigational product (placebo or efavaleukin alfa) at the week 12 visit. The exception will be placebo nonresponder subjects, who are defined as those randomized to placebo during the induction period and who failed to achieve clinical response at week 12. These placebo nonresponder subjects will be assigned in a blinded manner to receive [redacted] µg [redacted] dose during the long-term treatment period. Treatment assignment during the long-term treatment period will be done by interactive response technology (IRT) based on the modified Mayo score using the locally read endoscopy subscore assigned by the investigator (refer to Section 6.1.1.2).

During the long-term treatment period, subjects will be assessed for worsening of disease activity, defined by a partial Mayo score of ≥ 4 with an increase from week 12 in rectal bleeding subscore to ≥ 2 and/or an increase from week 12 in stool frequency subscore to ≥ 2. It is recommended that the investigator should determine whether a subject should discontinue investigational product based on worsening of disease activity, either based on the partial Mayo criteria above or their clinical judgement.

Subjects who were nonresponders at week 12, and who have an inadequate response by [redacted] will be discontinued from further investigational product administration in long-term treatment period.

Inadequate response is defined by failure to achieve a 2-point reduction and 25% improvement in partial Mayo score compared to the partial Mayo score at screening (and a minimum partial Mayo score of ≥ 5 points) at [redacted]

Efficacy evaluations during the long-term treatment period will include the total and partial Mayo score, fecal calprotectin, and corticosteroid use. The modified Mayo score (including endoscopy) and mucosal biopsies for histopathology will be assessed at the week 52/ early termination 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 [redacted] If a subject undergoes ET soon after having their week 12 endoscopy, the need for an ET endoscopy should be discussed with the Amgen physician.

Subjects who complete the week 52 endoscopy and who, in the opinion of the investigator, may benefit from continued treatment, will be assessed for eligibility to roll over into the Phase 2 Long Term Extension Study (20210210).

4.1.3 Safety Follow-up Period

The safety follow-up period consists of a single safety follow-up visit. [redacted]

[redacted]

4.2 Patient Input into the Study Design

Patient input was obtained for design of a study to treat UC. Two patient panels were queried to obtain insights to optimize study design and decrease patient burden.

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

In this study, subjects with moderately to severely active UC will be randomized to receive one of the following induction doses: [redacted] μg [redacted] μg [redacted] μg [redacted] or placebo [redacted] The planned induction doses were selected based on i) analyses of efavaleukin alfa pharmacokinetic (PK) and pharmacodynamic (PD) from completed and ongoing phase 1 studies to date ii) Treg data from a single arm open label study of low dose IL-2 in subjects with moderately to severely active UC (Allegretti et al, 2020) iii) safety data from completed and ongoing studies.

All planned doses have demonstrated acceptable safety in phase 1 studies (Please see Investigator's Brochure for further details). In addition, clinical results from studies of UC patients treated with low dose IL-2 suggest that UC patients may benefit from treatment with efavaleukin alfa (Allegretti et al, 2020). The highest proposed dose of [redacted] μg [redacted] was evaluated in a phase 1b study of subjects with SLE and was found to have acceptable safety and tolerability.

A subsequent dosing cohort of [redacted] μg [redacted] was also found to have acceptable safety and tolerability but has not been included in phase 2 studies due to an apparent plateau in fold-expansion of T regulatory cells and low-level fold-increase in other IL-2–responsive cells, although interpretation is limited due to small subject numbers. As of 26 April 2022, no deaths, life-threatening, or serious treatment emergent adverse events have been reported in these ongoing cohorts.

[redacted]. The PD has demonstrated dose-dependent, selective Treg expansion that peaks at day 8 post-dose with no meaningful expansion of CD4 Tcon, CD8 Tcells and NK cells. [redacted]

[redacted]

Based on exposure-Treg modeling of all available efavaleukin alfa phase 1 data, the [redacted] μg [redacted] dose is predicted to yield an approximate [redacted] in Tregs from baseline (Inter-quartile range [IQR] range: [redacted]); the [redacted] μg [redacted] dose is predicted to yield an approximate [redacted] in Tregs from baseline (IQR range: [redacted] the [redacted] μg [redacted] dose is predicted to yield an approximate [redacted] in Tregs number from baseline (IQR range: [redacted]).

The doses [redacted] μg [redacted] [redacted] μg [redacted] [redacted] μg [redacted] have been tested in the ongoing phase 1b study in subjects with SLE. Observed Treg expansion aligned with ranges predicted by exposure-Treg modeling. Peak Treg expansion at each dose was statistically differentiated from placebo and from each other dose. There were no statistically significant differences in CD4 Tcon expansion between efavaleukin alfa at any dose and placebo. The planned phase 2b doses are anticipated to test a differentiated range of Treg expansion in subjects with UC and will further inform our understanding of the target level of Treg expansion required for efficacy in this patient population.

Efavaleukin alfa SLE phase 1b Treg data were compared with Treg/clinical response data from a published study of low dose IL-2 in subjects with moderately to severely active UC. After 8 weeks of treatment, clinical response or remission was observed in 9 of 15 (or 60%) subjects treated with an effective dose of low dose IL-2 (Allegretti et al, 2020). The ranges of peak Treg expansion observed at efavaleukin alfa doses of greater than or equal to [redacted] μg in subjects with SLE are approximately comparable to peak blood Treg concentrations associated with clinical efficacy in subjects with UC treated with low dose IL-2 (Allegretti et al, 2020). This comparison may be limited by significant methodological differences and the assumption that subjects with SLE and UC will provide similar PD responses.

[redacted] dosing frequencies have been evaluated in 3 multiple-dose phase 1b studies and have been found to produce similar peak Treg expansion that was generally sustained over multiple doses. However, comparison of trough Treg concentrations across dosing frequency was inconclusive because of limited [redacted] data and large inter-subject variability. Once [redacted] dosing was selected for all doses in this phase 2b study because: 1) peak Treg concentrations are predicted to be similar

and sustained across multiple [redacted] and [redacted] dosing, and 2) [redacted] is predicted to yield blood Treg trough values approximately 2 weeks after dosing that remain well above baseline concentrations in the dose range proposed. These predictions are consistent with observed Treg data from RA, SLE, and cGvHD phase 1b studies. In addition, given the similarity in peaks and variability in [redacted] troughs, patient convenience was considered. Therefore, a [redacted] regimen was determined to be the optimal frequency for efavaleukin alfa in Study 20170104 based on current data.

The anticipated exposures for the planned doses are well below those that were observed at the NOAEL in the Good Laboratory Practice cynomolgus monkey toxicology studies, with maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) margins of 3 and 16.3, respectively, for the highest dose of [redacted] µg [redacted] Please see Investigator's Brochure for further details.

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 [redacted] (if applicable, see Table 1-4). The total study duration for an individual subject may be up to 61 weeks. This includes up to a 35-day screening period, 12 weeks of induction treatment, up to 40 weeks of long-term treatment, and a [redacted]

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, long-term follow-up), 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).

Eligibility criteria will be evaluated at the screening visit and at the day 1 visit prior to randomization.

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 provided.

5.1 Inclusion Criteria

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

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

102 Age ≥ 18 years to < 80 years at screening visit, except in South Korea where age ≥ 19 years to < 80 years at screening visit.

103 Diagnosis of UC established ≥ 3 months prior to enrollment by clinical and endoscopic evidence and corroborated by a histopathology report. If a histopathology report is not available at screening, then additional biopsies may be taken during the screening period for local histopathology analysis to corroborate.

104 Moderately to severely active UC as defined by a modified Mayo score of 5 to 9, with a centrally read endoscopy subscore ≥ 2.

105 Has documentation of

- A surveillance colonoscopy (performed according to local standard) within 12 months of day 1 visit for subjects with pancolitis of > 8 years duration, or subjects with left-sided colitis of > 12 years duration, or subjects with primary sclerosing cholangitis.
- For all other subjects, up-to-date colorectal cancer surveillance (performed according to local standard). At the discretion of the investigator, a colonoscopy (instead of a rectosigmoidoscopy) may be performed as the screening endoscopy for this study. Subjects who do not have a colonoscopy report available in source documentation will have a colonoscopy instead of rectosigmoidoscopy performed as the screening endoscopy for the study

106 Subjects must have demonstrated inadequate response, loss of response, or intolerance to at least 1 conventional therapy, biologic therapy, or targeted small molecule therapy (ie, JAK-inhibitor).

- Conventional therapy failed subjects:
  - Corticosteroids (corticosteroid-refractory colitis, defined as signs and/or symptoms of active UC despite oral prednisone (or equivalent) at doses of at least 30 mg/day for a minimum of 2 weeks; or corticosteroid-dependent colitis, defined as: an inability to reduce corticosteroids below the equivalent of prednisone 10 mg/day within 3 months of starting corticosteroids without a return of signs and/or symptoms of active UC; or a relapse within 3 months of completing a course of corticosteroids
  - History of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, or neuropsychiatric side-effects, including insomnia, associated with corticosteroid treatment)

- Immunomodulators: signs and/or symptoms of persistently active disease despite at least 3 months treatment with one of the following at locally approved doses: oral azathioprine (eg, ≥ 1.5 mg/kg/day) or 6-mercaptopurine (eg, ≥ 0.75 mg/kg/day), or oral azathioprine or 6-mercatopurine within a therapeutic range as judged by thioguanine metabolite testing, or a combination of a thiopurine and allopurinol within a therapeutic range as judged by thioguanine metabolite testing
- History of intolerance to at least 1 immunomodulator (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, and lymphopenia) and have neither failed nor demonstrated an intolerance to a biological medication (anti-TNF antibody, anti-integrin antibody, or IL-12/23 antagonists) that is indicated for the treatment of UC

- Biologic or targeted small molecule therapy failed subjects: those who demonstrated inadequate response or loss of response or intolerance to biologic therapy for UC (eg, anti-TNF antibodies or IL-12/23 antagonists, anti-integrin antibodies) or targeted small molecules (eg, JAK inhibitors or S1P modulators). The therapy used to qualify the subject for entry into this category must be approved for the treatment of UC in the country of use, at the time of use. Subjects must fulfil one of the following criteria:
  - Inadequate response: signs and symptoms of persistently active disease despite induction treatment at the approved induction dosing that was indicated in the product label at the time of use
  - Loss of response: recurrence of signs and symptoms of active disease during approved maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not quality as having failed or being intolerant to UC biological therapy or JAK inhibitor or S1P modulator)
  - Intolerance: history of intolerance to infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tofacitinib or other approved biologicals or JAK inhibitors or S1P modulators (including but not limited to infusion-related event, demyelination, congestive heart failure, or any other drug-related adverse event that led to a reduction in dose or discontinuation of the medication)

107 If receiving any of the following therapies, subjects must have stable dosage for the specified duration (refer to Section 11.9 for a summary of permitted medications):

- 5-aminosalicylates (ASAs), stable dosage for ≥ 2 weeks prior to screening endoscopy
- Oral corticosteroids: prednisone ≤ 20 mg/day or its equivalent, stable dose for ≥ 2 weeks prior to screening endoscopy
- Budesonide: extended-release tablets 9 mg/day [budesonide MMX], stable dose for ≥ 2 weeks prior to screening endoscopy
- Beclomethasone dipropionate: gastro-resistant prolonged-release tablet 5 mg/day, stable dose for ≥ 2 weeks prior to screening endoscopy
- Conventional immunomodulators: azathioprine, 6-mercaptopurine, methotrexate, stable dosage for ≥ 12 weeks prior to screening endoscopy

5.2 Exclusion Criteria

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

Disease Related

201 Diagnosis of Crohn's disease, inflammatory bowel disease-unclassified (indeterminate colitis), microscopic colitis, ischemic colitis, or clinical findings suggestive of Crohn's disease.

202 Disease limited to the rectum (ie, within 15 cm of the anal verge).

203 Evidence of toxic megacolon, fulminant colitis, intra-abdominal abscess, or stricture/stenosis within the small bowel or colon.

204 Previous bowel resection or intestinal or intra-abdominal surgery.

- Have had extensive surgery for UC (for example, subtotal colectomy), or are likely to require surgery for the treatment of UC during the study. Subjects who have had limited surgery for UC (for example, segmental colonic resection) may be allowed in the study, if this does not affect the assessment of efficacy. Discussion with the sponsor must occur prior to screening of such subjects.
- Have had any small bowel or colonic surgery within 6 months of day 1.
- Have had any nonintestinal intra-abdominal surgery within 3 months of day 1.

205 Adenoma and dysplasia exclusion criteria:

- Any current sporadic adenoma without dysplasia (adenomatous polyps occurring proximal to known areas of colitis) that has not been removed. Once completely removed, the subject is eligible for study.
- Dysplasia occurring in flat mucosa, sporadic adenomas containing dysplasia, and dysplasia-associated lesions or masses will be managed as follows:
  - Any history or current evidence of high-grade dysplasia.
  - Any history or current evidence of dysplasia occurring in flat mucosa. This includes histopathology reporting indefinite for dysplasia, low-grade dysplasia, and high-grade dysplasia.
  - Any history or current evidence of a nonadenoma-like dysplasia-associated lesions or masses, with or without evidence of dysplasia.
  - Any current sporadic adenoma containing dysplasia or any current adenoma-like dysplasia-associated lesions or masses that has not been removed. Once completely removed, the patient is eligible for the study.

206 Stool positive for *Clostridium difficile* toxin at screening and other enteric pathogens including but not limited to ova, parasites, Campylobacter, salmonella, shigella, *E coli* 0157:H7, and *Yersinia enterocolitica*.

207 History or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behavior based on an assessment with the Columbia Suicide Severity Rating Scale (C-SSRS) at screening.

Other Medical Conditions

208 Active infection (including chronic or localized infections) for which anti-infectives were indicated within 2 weeks prior to screening visit OR presence of serious infection, defined as requiring hospitalization or intravenous (IV) anti-infectives within 8 weeks prior to screening visit.

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

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

211 Any history of malignancy with the following exceptions:

- Resolved non-melanoma skin cancers > 5 years prior to screening.
- Resolved cervical in situ carcinoma > 5 years prior to screening.

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

- Poorly controlled diabetes or hypertension
- Chronic kidney disease stage IIIb, IV, or V
- Symptomatic heart failure (New York Heart Association class II, III or IV)
- Myocardial infarction or unstable angina pectoris within the past 12 months prior to day 1
- Severe chronic pulmonary disease requiring oxygen therapy
- Major chronic inflammatory disease or connective tissue disease other than UC (eg, rheumatoid arthritis)

213 Positive for hepatitis B surface antigen (HBsAg); or positive for hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) in the presence of detectable viral DNA in peripheral blood, assessed by polymerase chain reaction (PCR). Subjects positive for HBcAb and/or HBsAb without history of prior vaccination and without detectable serum hepatitis B viral DNA by PCR are allowed to enroll, provided the subject undergoes monitoring of serum hepatitis B viral DNA by PCR at every 2 months during the treatment period and up to 6 weeks after the end of treatment for the study. Subjects with a history of hepatitis B vaccination without history of hepatitis B infection (ie, positive HBsAb, negative HBsAg, and negative HBcAb) are allowed to enroll.

214 Positive for hepatitis C antibody (HCAb) in the presence of detectable viral RNA in peripheral blood, assessed by PCR. Subjects positive for HCAb without detectable viral RNA by PCR are allowed to enroll.

215 Known history of Human Immunodeficiency Virus (HIV) or positive HIV test at screening.

216 Inherited immunodeficiency syndrome.

217 Required systemic corticosteroid use for any indication other than UC. The only exception is corticosteroids used for the treatment of adrenal insufficiency are allowed.

218 Have had a bone marrow or solid organ transplantation.

219 Have had extra-abdominal surgery without full recovery prior to screening.

Prior/Concomitant Therapy (refer to Section 11.8 for a summary of prohibited medications):

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

221 Currently receiving or had treatment with recombinant IL-2 (eg, Proleukin®).

222 Corticosteroid enemas, corticosteroid suppositories, a course of intravenous corticosteroids or intramuscular corticosteroids, or oral budesonide standard formulation within 2 weeks prior to screening endoscopy.

223 5-ASA enemas or 5-ASA suppositories within 2 weeks prior to screening endoscopy.

224 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 last dose of investigational product in the study.

225 Has received any of the following prescribed medication or therapy within the specified time period:

- Anti-TNF antibodies (eg, infliximab, adalimumab, golimumab) $\leq$ 8 weeks prior to screening endoscopy
- Anti-integrin antibodies (eg, vedolizumab) < 8 weeks prior to screening endoscopy
- IL-12/23 antagonist (eg, ustekinumab) < 8 weeks prior to screening endoscopy
- JAK inhibitors (eg, tofacitinib) < 4 weeks prior to screening endoscopy
- S1P modulators (eg, ozanimod) < 4 weeks prior to screening endoscopy.

- Any other commercially approved biologic agent or targeted small molecule ≤ 8 weeks prior to screening endoscopy or < 5 half-lives prior to screening endoscopy, whichever is longer
- Immunomodulatory medications oral cyclosporine, IV cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, thalidomide < 4 weeks prior to screening endoscopy
- Any investigational biologic therapy within 8 weeks prior to screening endoscopy or < 5 half-lives prior to screening endoscopy, whichever is longer
- Have used apheresis (eg, Adacolumn® apheresis) < 2 weeks prior to screening endoscopy

Diagnostic Assessments

226 Abnormal laboratory results at screening:

- aspartate aminotransferase (AST) or alanine amino transferase (ALT) at screening > 1.5 X upper limit of normal (ULN)
- serum total bilirubin (TBL) ≥ 1.5 mg/dL (≥ 26 μmol/L)
  - Subjects with established diagnosis of Gilbert's syndrome are allowed if TBL ≤ 3X ULN (source documentation demonstrating unconjugated hyperbilirubinemia and no evidence of hemolysis required).
- hemoglobin ≤ 8.5 g/dL (≤ 85 g/L)
- platelet count < 100 000/mm^3 (< 100 x 10^9/L)
- white blood cell count < 3000 cells/mm^3 (< 3.0 x 10^9/L)
- absolute neutrophil count (ANC) < 1500/mm^3 (< 1.5 x 10^9/L)

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

Prior/Concurrent Clinical Study Experience

228 Currently receiving treatment in another investigational device or drug study

229 Ending 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.

Other Exclusions

230 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during study and for an additional 6 weeks after the last dose of investigational product. Subjects who suspend breastfeeding prior to starting treatment with the study drug and do not intend to resume breastfeeding within 6 weeks after receiving the last dose of investigational product can be enrolled.

231 Females of child-bearing potential (Section 11.5) with a positive pregnancy test (assessed by a serum pregnancy test at screening and a urine pregnancy test at day 1)

232 Female subject of childbearing potential unwilling to use at least 1 protocol specified method of contraception (Section 11.5) during treatment and for an additional 6 weeks after receiving the last dose of investigational product

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

234 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.

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

236 Current history of alcohol dependence and/or drug abuse within 1 year of day 1.

237 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.

5.3 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 (ICF), 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 investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the Subject Enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the ICF) 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 be the same as the randomization numbers assigned for the study.

Sites that do not enroll subjects within 6 months of site initiation may be closed.

5.4 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. Refer to Section 8.1.1 for rescreen procedures.

5.5 Eligibility Requirements for Progression to Long-term Treatment

Subjects enrolled in the induction period who complete the week 12 visit and who have not discontinued investigational product will have the option to continue to be treated in the exploratory long-term treatment period if in the opinion of the investigator they would benefit from further treatment.

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) described in Section 6.1.1 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).

A summary of the dosing and administration of each treatment is shown below.

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.

Efavaleukin alfa or placebo will be administered by SC injection in the abdomen, thigh or upper arm by authorized site personnel on day 1. 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 the window of time specified for the scheduled time point (see Schedule of Activities Table 1-1, Table 1-2, and Table 1-3) and any 2 consecutive doses of investigational product must be at least 7 days apart. If that window is missed, that dose will not be administered, and the next dose will be administered at the next scheduled dosing date. Note: For subjects continuing in the long-term treatment period (Section 6.1.1.2), investigational product administration at

week 12 has a dosing window up to + 3 days after the week 12 visit to allow for dosing on a separate day from the endoscopy.

[redacted] Subjects who will continue to receive investigational product in the long-term treatment period [redacted]

For each vial, the 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).

6.1.1.1 Dose Administration and Schedule in the Induction Period

The placebo and efavaleukin alfa doses will be administered by SC injection [redacted] starting on day 1 through week 12. The following treatment groups are planned:

- Placebo [redacted]
- Efavaleukin alfa [redacted] µg [redacted]
- Efavaleukin alfa [redacted] µg [redacted]
- Efavaleukin alfa [redacted] µg [redacted]

6.1.1.2 Dose Administration and Schedule in the Long-term Treatment Period

Subjects will continue to receive their assigned blinded dose of investigational product (placebo or efavaleukin alfa) beginning at the week 12 visit. The exception will be placebo nonresponder subjects, who are defined as those randomized to placebo during the induction period and failed to achieve clinical response at week 12. These placebo nonresponder subjects will be assigned in a blinded manner to receive [redacted] µg [redacted] dose during the long-term treatment period (Table 6-1). For the purposes of treatment assignment into the long-term treatment period, clinical response is defined as a decrease from baseline in the modified Mayo score (using the endoscopic subscore assigned by the investigator) of ≥ 2 points and at least 30% reduction from baseline, and a decrease in the rectal bleeding subscore of ≥ 1 or an absolute rectal bleeding subscore of 0 or 1.

Table 6-1. Investigational Product Administration: Long-term Treatment Period

Investigational Product Administration	
Induction Period	Long-term treatment period

Day 1 to Week 12	Week 12 up to Week 52 or Early Termination
Placebo [redacted] responder[a, d]	Placebo [redacted]
Placebo [redacted] nonresponder[b, d]	[redacted] µg [redacted]
[redacted] µg [redacted] [d]	[redacted] µg [redacted]
[redacted] µg [redacted] [d]	[redacted] µg [redacted]
[redacted] µg [redacted] [d]	[redacted] µg [redacted]
[redacted]	

[a] A placebo responder subject is one who achieved clinical response at week 12.
[b] A placebo nonresponder subject is one who did not achieve clinical response at week 12.
[c] Subjects randomized to efavaleukin alfa will remain on the same dose through the long-term treatment period and includes responders and nonresponders.
[d] Clinical response for the purpose of treatment assignment in the exploratory long-term treatment period will be assessed using the modified Mayo score and the endoscopic subscore assigned by the investigator.

Subjects who were nonresponders at week 12, and who have an inadequate response by week [redacted] will be discontinued from further investigational product administration in long-term treatment period (Section 4.1.2).

6.1.2 Medical Devices

No investigational medical devices will be used in the 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-required Therapies

All other protocol-required therapies that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Concomitant medications are described in Section 6.7.2.

6.1.4 Other Intervention Procedures

6.1.4.1 Home Health Care Visits

Section 6.1.4.1 is not applicable for participating sites in Bulgaria.

If permitted by local regulations, the investigator may utilize a qualified home health care service provider, approved by sponsor, for collection of PK, biomarker samples and electrocardiogram (ECG) on visits without a scheduled administration of investigational

product. In addition to PK, biomarker sample, and ECG collection, safety and concomitant medications data collection will be conducted.

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 or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

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

Any product complaint(s) associated with efavaleukin alfa/placebo 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:

- Any other investigational therapies or device
- T cell depleting agents (eg, antithymocyte globulin, Campath)
- Recombinant IL-2 (eg, Proleukin)
- Other immunomodulatory agents (including but not limited to cyclosporine, mycophenolate mofetil, tacrolimus, sirolimus)

The following medications are prohibited unless the subject has stopped investigational product permanently:

- Commercially available biologic agents (eg, vedolizumab, ustekinumab, antiTNFs [infliximab, adalimumab, or golimumab]) or biosimilars to these agents
- Targeted small molecules (eg, S1P modulators or JAK inhibitors)
- IV or intramuscular corticosteroids
- Live vaccines (prohibited up to 6 weeks after the last dose of investigational product in the study)
- Steroid or aminosalicylate based enemas

6.2 Dose Modification

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

No dose group or cohort escalations are included in this study.

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 during the study. Subjects will be permanently discontinued from investigational product if they initiate excluded treatments as described in Section 6.1.6 at any time during the study.

Refer to Section 7 for handling permanent discontinuation of 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

Both efavaleukin alfa and placebo 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.

Guidance and information on drug accountability for the investigational products will be provided to the site.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

6.4.1.1 Subject Randomization

At day 1, subjects will be randomized in a 1:1:1:1 ratio to placebo or 1 of the 3 efavaleukin alfa dose parallel groups in a double-blind manner. The randomization will be stratified by prior experience with at least 1 biologic or targeted small molecule (yes/no) and corticosteroid use at randomization (yes/no).

The randomization will be performed by IRT.

The randomization date is to be documented in the subject's medical record and on the Subject Enrollment CRF (via IRT).

During the long-term treatment period, subjects will be assigned to receive the same blinded treatment as received during the induction period, except for placebo nonresponder subjects who will be assigned to receive efavaleukin alfa (Table 6-1). The treatment assignment will be performed by IRT.

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 until all subjects have had the opportunity to complete the week 12 visit and the primary analysis has been completed.

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. The unblinding of treatment assignment will be performed via IRT.

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 (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 6.4.2.1).

6.5 Treatment Compliance

When subjects are dosed at the site, they will receive investigational product directly from the investigator or designee, under medical supervision. The date and time of each

dose administered in the clinic 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; therefore, no known treatment of overdose.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior therapies that were being taken from 5 years of enrollment through the date of randomization should be collected. Therapy name, dose, unit, frequency, start date, and stop date should be collected.

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 Section 6.1.6 (summarized in Section 11.8).

Concomitant therapies are to be collected from randomization through the end of study. For concomitant therapies being taken for UC, collect therapy name, indication, dose, unit, frequency, start date, stop date and reason for stopping. For all other concomitant therapies, collect therapy name, indication, dose, unit, frequency, start date, and stop date.

6.7.2.1 Induction Period

The following treatments for UC may not be initiated or have dose increased through end of the induction period (Section 5.1):

- Oral 5-ASA compounds (eg, sulfasalazine, mesalamine)
- Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate)
- Oral corticosteroids including budesonide MMX or beclomethasone dipropionate (gastro-resistant prolonged-release tablet)

Subjects who are receiving any of these treatments for UC at day 1 must keep their prescribed dosage stable throughout the induction period and the therapy can only be discontinued or reduced in dose if in the investigator's clinical judgment it is required because of toxicity or other medical necessity; even if the toxicity resolves, the therapy must not be restarted.

6.7.2.2 Long-term Treatment Period

The following UC-specific medical therapies must not be initiated or have the dose increased during the long-term treatment period:

6.7.2.2.1 Oral 5-ASA Compounds

Oral 5-ASA therapy may not be initiated during long-term treatment period (stable dose is encouraged).

6.7.2.2.2 Immunomodulators

Immunomodulators (6-mercaptopurine, azathioprine, or methotrexate): Subjects who were receiving any of these medical therapies for UC at the time of entry into the long-term treatment period and do not experience disease worsening must keep their prescribed dosage stable through completion of the long-term treatment visits unless in the investigator's clinical judgment these require discontinuation or dose reduction because of toxicity or other medical necessity; even if the toxicity resolves, the therapy must not be restarted.

6.7.2.2.3 Corticosteroids

For subjects in clinical response or clinical remission (as assessed at week 12 by the modified Mayo score using locally read endoscopy subscore), who are receiving oral corticosteroids on entry into the long-term treatment period, the investigator must begin tapering the daily dose of corticosteroids at the week 12 visit.

Recommended tapering schedule is as follows:

- For prednisone at doses > 10 mg/day (or equivalent), the dose should be reduced at a rate of 5 mg per week until a 10 mg/day dose is reached.
- For prednisone at doses ≤ 10 mg/day (or equivalent) or once a 10 mg/day dose (or equivalent) is achieved by tapering, the dose should be reduced at a rate of 2.5 mg/week until discontinuation.
- For budesonide MMX, the dose should be tapered at a rate of 3 mg every 3 weeks until discontinuation.
- For beclomethasone dipropionate (gastro-resistant prolonged-release tablet), the dose should be tapered to 5 mg every other day for 4 weeks and then discontinued.

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 below.

7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized 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 1-1, Table 1-2, Table 1-3, and Table 1-4) 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 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) may include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance

- Pregnancy
- Requirement for alternative therapy
- Protocol-specified criteria:
  - A colectomy (partial or total) or an ostomy
  - Inadequate response per the partial Mayo score at [redacted] (for week 12 nonresponders only) (see Section 4.1.2)
  - Disease-worsening per the partial Mayo score during the long-term treatment period (see Section 4.1.2)

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 1-2, Table 1-3, and Table 1-4) 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

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 are 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 Schedule of Activities (Table 1-1, 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

Visit assessments for screening, enrollment, randomization, and day 1 dose administration will occur per the Schedule of Activities (Table 1-1).

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the ICF, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 35 days prior to first dose of investigational product.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

A subject must be in screening for at least 14 days prior to day 1 to enable a minimum of 7 days of Mayo daily symptom diary collection prior to the screening endoscopy and to

enable results from the central reader assessment of the endoscopy to be received prior to the day 1 visit. Stool frequency and rectal bleeding Mayo subscore calculation, laboratory results from blood collection, stool collection, and urinalysis results must have been received and confirmed eligible prior to subject proceeding to screening endoscopy.

Mayo daily symptom diaries will be provided to each subject to record stool frequency and episodes of rectal bleeding. The daily diaries will be completed from screening and will be used to calculate the stool frequency and rectal bleeding Mayo subscores (Section 8.3.1) to assess the subject's eligibility for further screening and to train the subject on the use of the daily diary (Section 8.3.1.1). Subjects with a combined stool frequency and rectal bleeding subscore ≥ 2 (using the average of the 3 most recent days in the 7 days prior to initiation of bowel preparation for the screening endoscopy) can proceed with **endoscopy** (Section 8.3.1.2). Subjects who do not have an up-to-date colorectal cancer surveillance colonoscopy in source document will have a colonoscopy instead of a rectosigmoidoscopy at screening as per inclusion criteria 105.

The following laboratory parameters may be retested twice during the 35-day screening period: hematology, chemistry, urine analysis, stool samples for *C. difficile* and other enteric pathogens, indeterminate interferon gamma release assay for TB. Under special circumstances the endoscopy may be repeated when, for example there is poor visualization of the enteric mucosa due to poor bowel preparation or because of technical issues with video recording equipment.

At the 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 day 1 visit, the subject will be registered in IRT as a screen failure. Screen fail subjects may be eligible for re-screening 2 times. Subjects that are positive for HBsAg or positive for hepatitis C antibody as per exclusion criteria (213 and 214) or positive for HIV (exclusion criterion 215) will not be allowed to re-screen.

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 35-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening.

If the rescreening period begins more than 35 days after the most recent signed informed consent form, then a new informed consent form must be signed.

Eligible screening assessments from previous screening periods may be used if the assessment was performed within 35 days prior to randomization with the following exceptions and clarifications:

- Tuberculosis screening tests (QuantiFERON®-TB, T-spot test OR positive PPD), serologies for hepatitis B virus, hepatitis C virus and HIV, provided that the rescreening occurs ≤ 12 months of screening visit and there is no patient's medical/epidemiological history suggestive of infection or recent exposure in cases of infection.
- If subject had received a course of antibiotics for *C difficile* toxin or another enteric pathogen, then subject must have discontinued antibiotic treatment for *C difficile* or other enteric pathogen at least 30 days prior to rescreening and testing for *C difficile* toxin or other enteric pathogens must be repeated. It is recommended that local testing for *C difficile* toxin and other pathogens occur before rescreening to confirm negative status.

8.1.2 Induction Period

Visits during the induction period will occur per the Schedule of Activities (Table 1-2). On-study visits must be completed within ± 5 days. 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. All patient reported outcomes (PROs) must be completed before any other study procedures for each visit. The investigational product is to be administered following the completion of all other study-required procedures for each visit.

8.1.3 Long-term Treatment Period

Visits during the exploratory long-term treatment period will occur per the Schedule of Activities (Table 1-3). On-study visits may be completed within ± 5 days. All PROs must be completed before any other study procedures for each visit. The investigational product is to be administered following the completion of all other study-required procedures for that visit, inclusive of the long-term treatment period assessments.

8.1.4 Safety Follow-up Period

A single safety follow-up visit may be required at [redacted] per the Schedule of Activities (Table 1-4). Refer to Section 4.1.3.

8.2 General Assessments

8.2.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC and Amgen 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 prior to enrollment or as necessary to describe chronic or co-morbid conditions through the start of the adverse event reporting period. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, UC history must date back to the original diagnosis. Normal stool frequency data will also be collected. The current toxicity grade will be collected for each condition that has not resolved.

8.2.4 Physical Examination

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

8.2.5 Physical Measurements

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

8.2.6 Substance Abuse History

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

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

8.2.7 Columbia Suicide Severity Rating Scale

The baseline version of the C-SSRS will be administered at screening.

The C-SSRS is a clinician rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items, which defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The C-SSRS will be administered by the principal investigator or qualified designee. Reports of suicidal

ideation with intent to act (severity of 4 or 5) and reports of actual, aborted, or interrupted suicide attempts or a behavior preparatory for making an attempt indicate subjects at high risk for suicide. If such reports are identified at screening, it is an exclusion criterion and the subject is not eligible for the study.

8.3 Efficacy Assessments

Specific efficacy assessments and time points are summarized in the Schedule of Activities (Table 1-1, Table 1-2, and Table 1-3).

8.3.1 Mayo Score (Total, Modified, and Partial)

The total Mayo score is a composite index of 4 items (stool frequency, rectal bleeding, endoscopy findings, and physician's global assessment) with each item graded semi-quantitatively on a score of 0 to 3 for a maximal total score of 12. Scores range from 0 to 12 points. The Mayo Daily Symptom Diary will be used to record stool frequency and rectal bleeding. Refer to Appendix 10 for full definitions of Mayo subscores.

The modified Mayo score is the Mayo score without the physician's global assessment subscore and ranges from 0 to 9 points. The modified Mayo score will be used to assess primary and secondary efficacy endpoints.

The partial Mayo score is the total Mayo score without the endoscopy subscore and ranges from 0 to 9 points.

The rectal bleeding and stool frequency subscores will be derived from the last 3 days of data entered within the last 7 days prior to the visit, or within 7 days prior to initiation of bowel preparations for visits which include an endoscopy.

Calculation of the modified Mayo score at screening to determine eligibility must use the stool frequency and rectal bleeding diary data from the most recent 3 days within the 7 days prior to initiation of bowel preparations for the eligible screening endoscopy. Bowel preparations should not be initiated if the combined sum of the rectal bleeding subscore and stool frequency subscore is not ≥ 2. Refer to Appendix 10 for Mayo Scoring System for the Assessment of Ulcerative Colitis Activity.

8.3.1.1 Mayo Daily Symptom Diary

Mayo daily symptom diaries will be provided to each subject to record stool frequency, and episodes of rectal bleeding. Subjects will be instructed to complete the diary daily except upon commencing bowel preparation for endoscopy. Recommence daily diary entries upon completion of the endoscopy.

8.3.1.2 Endoscopy

For the purposes of this study, a rectosigmoidoscopy or colonoscopy will be performed as part of the total and modified Mayo Score. At the week 12 and 52/ET visits, a colonoscopy can be performed instead of rectosigmoidoscopy for clinically indicated reasons in the judgement of the investigator and after discussion with the Amgen physician as appropriate. The procedure can be performed by the investigator or qualified designee using the institution's standard procedure and study manual. The screening endoscopy must be performed approximately 14 days and no sooner than 5 days (to enable results from the endoscopy central reader to be obtained and reviewed by the site) prior to the day 1 visit. Subjects who do not have an up-to-date colorectal cancer surveillance colonoscopy in source document will have a colonoscopy instead of a rectosigmoidoscopy at screening per inclusion criteria 105.

All rectosigmoidoscopies (or if applicable colonoscopy) will be read locally by the investigator (or designee). In addition, video-recording of rectosigmoidoscopies (or if applicable colonoscopy) performed at screening, week 12, and at the week 52 visit, will be sent to a central reader for determination of the endoscopic component of the Mayo score. Separate instructions on procedures and data collection for central reading of rectosigmoidoscopies will be provided to the site. Central reading assessment at screening, week 12, and week 52 visit will be combined with the site assessment of clinical indices of the Mayo score (stool frequency, rectal bleeding, physician’s global assessment) to compute the total or modified Mayo score (without the physician's global assessment) for that given visit.

Rectosigmoidoscopies (or if applicable colonoscopies) performed at early termination will require central reading.

For the purposes of treatment assignment into the long-term treatment period, clinical response will be assessed using the modified Mayo score and the endoscopic subscore assigned by the investigator (refer to Section 6.1.1.2).

8.3.1.3 Physician’s Global Assessment

The physician’s global assessment acknowledges the 3 other Mayo subscores, the patient’s recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient’s performance status.

8.3.2 Histopathology via Mucosal Biopsy

Biopsy specimens for evaluation of the histologic endpoints will be obtained from the area of most severe inflammation in the colon. Refer to the Laboratory Manual for further details on collection and processing of mucosal biopsies.

The histopathologic images will be read centrally in a blinded manner by a qualified pathologist, and scoring will be performed by using the Geboes Score. Refer to histopathology central reading charter for further details.

The Geboes score is an instrument that is used to standardize histologic assessment in UC. It comprises 7 categories (or grades), each of which describes a histologic feature. These categories are as follows: grade 0, structural (architectural change); grade 1, chronic inflammatory infiltrate; grade 2A, lamina propria eosinophils; grade 2B, lamina propria neutrophils; grade 3, neutrophils in epithelium; grade 4, crypt destruction; and grade 5, erosion or ulceration. Each grade includes subscores that indicate the degree of abnormality seen for that histologic feature, with subscores of 0 indicating normal appearance and higher subscores indicating increasingly abnormal appearance (Geboes et al, 2000).

8.3.3 Clinical Outcome Assessments

Any PROs administered according to the Schedule of Activities must be completed before any other study procedures, including assessment of weight. Patient reported outcomes (PROs) will be administered on an electronic device.

8.3.3.1 [redacted]

[redacted]

8.3.3.1.1 [redacted]

8.3.3.1.2 [redacted]

8.3.3.1.3 [redacted]

8.3.3.2 Inflammatory Bowel Disease Questionnaire

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a disease specific PRO instrument that measures health-related quality of life in patients with IBD (Guyatt et al, 1989). The IBDQ has been designed to be self-administered and completed in 15 minutes by respondents ≥ 18 years of age. The IBDQ covers the following dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items) and social function (5 items). Items are scored on a 7-point Likert scale, yielding a global score in the range 32 to 224 (with higher scores indicating better quality of life).

8.3.3.3 EQ-5D-5L

The EuroQol-5-Dimension 5 levels (EQ-5D-5L) questionnaire is a 2-page, standardized instrument for use as a measure of health outcome developed by the EuroQol group

(Rabin and de Charro, 2001). It is comprised of a 5-dimension health status measure and a visual analogue scale. The 5-dimension health status measure evaluates: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression based on a 5-level scale: no problems, slight problems, moderate problems, severe problems, an extreme problem. The visual analogue scale records the subject's self-rated health on a vertical, the visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. The EQ-5D-5L takes about 3 minutes to complete.

8.3.3.4 Patient Global Impression of Change

Patient perceived change since the start of treatment will be measured using the 'Patient Global Impression of Change (PGIC)'. Specifically, the PGIC captures patient perceived change in their UC symptoms since the start of treatment. In addition, it can be used as an anchor to estimate the minimally important difference as well as the small, medium, and large changes detected by other instruments.

8.3.3.5 Patient Global Impression of Severity

Patient perceived disease severity will be assessed using the 'Patient Global Impression of Severity (PGIS)'. Specifically, the PGIS captures patient perceived impression of severity of their UC symptoms. In addition, the PGIS can be used as an anchor in differentiating clinically distinct groups of subjects.

8.4 Safety Assessments

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

8.4.1 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, tympanic, axilla, or forehead (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.

8.4.2 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.

8.4.3 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 1-1, 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 Event 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 clinical judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

Fecal calprotectin, fecal lactoferrin, high sensitivity C-reactive protein (hsCRP), central histology reads, antibody, PK, and lymphocyte subsets that are collected after randomization and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.4.3.1 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 tuberculosis test (ie, positive PPD or positive or indeterminate QuantiFERON®-TB or T-spot test).

8.4.3.1.1 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. Purified protein derivative (PPD) test kits will not be provided by the sponsor and must be procured locally.

8.4.3.1.2 QuantiFERON®-TB or T-Spot Testing

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

8.4.3.2 HIV Antibodies, Hepatitis B, and Hepatitis C Testing

HBsAb, HBsAg, HBcAb, HCAb, and HIV antibodies (where permitted by local regulations) will be assessed at screening. If the results show a negative HBsAg and positive HBcAb and/or HBsAb, quantification of serum hepatitis B virus DNA by PCR is necessary. Similarly, if the results show a positive HCAb, a quantification of serum hepatitis C virus RNA by PCR is necessary. The above-mentioned PCR test results must be negative at screening for the subject to be eligible for this study. Subjects positive for HBcAb and/or HBsAb without history of prior vaccination and without detectable serum Hepatitis B viral DNA by PCR are allowed to enroll, provided the subject undergoes monitoring of serum Hepatitis B viral DNA by PCR at every 2 months during the treatment period and up to 6 weeks after the end of treatment for the study. Subjects with a history of hepatitis B vaccination without history of hepatitis B infection (ie, positive HBsAb, negative HBsAg, and negative HBcAb) are allowed to enroll.

8.4.3.3 Fecal Calprotectin, Fecal Lactoferrin, C Difficile Toxin and Enteric Pathogen Testing

Whole stool specimens will be collected within the 3 days prior to or during the study visit for quantitative determination of fecal calprotectin and fecal lactoferrin levels. Stool samples must be collected prior to preparation of bowel for endoscopies. Stool samples will be delivered to the sites by the subjects, and subsequently processed and shipped to the central laboratory for testing. Detailed sample collection instructions for the subjects, and sample processing and shipping instructions for the sites, will be provided in the central laboratory manual. Fecal calprotectin or lactoferrin information that would potentially unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Stool specimens will be tested at screening for *C difficile* toxin and other enteric pathogens including ova, parasites, Campylobacter, salmonella, shigella, *E. Coli* 0157:H7, and *Yersinia enterocolitica* as specified in the laboratory manual.

Stool sample must be collected and results available before the day 1 visit.

8.4.4 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.

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

8.4.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) 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 first dose of investigational product through the end of study are reported using the Events eCRF.

8.4.4.1.2 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 the end of study 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.

8.4.4.1.3 Serious Adverse Events After the Protocol Required Reporting Period

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 these serious adverse events will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the events.

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 after the subject ends the study.

8.4.4.2 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.

8.4.4.3 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.

8.4.4.4 Regulatory Reporting Requirements for Safety Information

If subject is permanently withdrawn from investigational product(s), and/or non-investigational product(s)/auxiliary medicinal product(s) 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 (SUSAR) 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.

8.4.4.5 Safety Monitoring Plan

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

8.4.4.6 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 investigational product.

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, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 11.5.

Pregnancy Testing

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

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see [redacted]. Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing using a high sensitivity urine pregnancy test should be performed at every 4 week intervals during treatment with investigational product and at the follow-up safety assessment and recorded on the eCRF.

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

8.5 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 1-1 and Table 1-2).

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

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

8.6 Pharmacogenetic Assessments (Optional Consent)

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 this/these analysis/analyses, DNA may be extracted.

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

8.7 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Table 1-1, Table 1-2, Table 1-3, and Table 1-4) for the measurement of anti-efavaleukin alfa antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized. Additional blood samples may be obtained to rule out anti-efavaleukin alfa antibodies during the study.

Subjects who test positive for anti-efavaleukin alfa antibodies that cross-react with and neutralize native human IL-2 at the final scheduled study visit will be asked to return for additional follow up testing. This testing is to occur approximately every 3 months starting from the final scheduled antibody point and continue until: (1) IL-2 neutralizing antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of efavaleukin alfa. All follow-up results, both positive and negative will be communicated to the sites. This notification is independent of and may be in advance of the time point when the entire study is unblinded. Notification of a requirement for antibody follow-up testing is not unblinding since both placebo and dosed subjects will be monitored for antibodies using the same testing scheme, and binding and neutralizing antibodies to IL-2 are known to exist in healthy subjects and subjects with autoimmune disease (Shao and Gao, 2019; Perol et al, 2016; Watanabe et al, 2007; Balsari and Caruso, 1997).

More frequent testing or testing for a longer period of time may be requested in the event of safety-related concerns.

Refer to the laboratory manual for detailed collection and handling instructions.

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 Pharmacodynamic Assessments

Samples will be collected to understand the mechanism of action and biological effects of administration of efavaleukin alfa.

Lymphocytes subsets: Blood samples will be collected for all subjects at the time points indicated in the Schedule of Activities (Table 1-1, Table 1-2, and Table 1-3). These samples will be used to evaluate the fold changes from baseline of Treg, CD4+ Tcon, CD8+ T cells, and NK absolute cell counts (cells/μL) after efavaleukin alfa administration.

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

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

Biomarker mucosal biopsy: Biopsy for biomarker development will be performed at the time points indicated in the Schedule of Activities (Table 1-1, Table 1-2, and Table 1-3). Biopsy specimens for biomarker development will be obtained at the same time as the mucosal biopsy for histologic assessment. Refer to Section 11.6 for more information.

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 at the time points specified in 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 the inflammatory conditions.

8.9 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of UC-related medical care encounters, including surgeries (eg, colectomy), and other selected procedures (inpatient and outpatient)
- Duration of UC-related hospitalization (total days or length of stay)

9. Statistical Considerations

9.1 Statistical Hypotheses

The primary hypothesis is that at least 1 efavaleukin alfa dose will have greater efficacy compared to placebo as measured by clinical remission rate at week 12 in subjects with moderately to severely active UC.

9.2 Sample Size Determination

The planned sample size of 240 subjects provides approximately [redacted]

9.3 Populations for Analysis

Population	Description
Full Analysis Set	All subjects randomized, analyzed by planned treatment group
Safety Analysis Set	All subjects randomized and received at least 1 dose of investigational product, analyzed by actual treatment group

9.3.1 Covariates

The impact of 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 include, but are not limited to the following:

- Stratification factors
  - Prior experience with at least 1 biologic or targeted small molecule: (yes, no)
  - Corticosteroid use at randomization: (yes, no)
- Age (< 40 years, ≥ 40 years)
- Sex (female, male)
- Race (white, non-white)
- Geographic region (Eastern Europe, Asia Pacific, Rest of World)
- Mayo score at baseline
- Disease localization (proctosigmoiditis, left-sided colitis, extensive colitis, pancolitis)
- Duration of UC (years from date of diagnosis to first dose date)

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.

9.3.2 Subgroups

In addition to stratification factors, some covariates, not limited to those mentioned in Section 9.3.1, may be used for further exploration in subgroups.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

Interim analyses will be conducted to assess for futility. Interim analyses will be conducted by an external Independent Biostatistics Group and results evaluated by an independent DMC (Section 11.3). In the case where prespecified decision rules are met at a planned interim analysis, Amgen may review the unblinded results to endorse a final decision. Details will be described in a Data Access Plan.

[redacted]

Data from the interim analyses may also be analyzed to support dose selection or other activities related to further development, prior to the primary analysis. The interim data will be analyzed by an internal Amgen team, separate from the study team. Measures will be taken and documented to ensure these individuals who access restricted data for this purpose are separate from the study team.

Data will be subject to ongoing checks for integrity, completeness and accuracy in accordance with the Data Management Plan with the expectation that outstanding data issues are resolved ahead of each interim analysis to the extent possible.

In addition to the planned interim analyses, the DMC will regularly review the accumulating safety data to ensure the continuing safety of study subjects. The first 2 DMC meetings will occur after the first 20 subjects randomized have had the opportunity to complete the [redacted] and week 12 visits. Thereafter the DMC will plan to meet approximately every 3 months until Amgen is unblinded at the primary analysis. After Amgen is unblinded, the DMC will plan to meet every 6 months. Ad hoc meetings can be scheduled as needed. The DMC will also review all available safety and efficacy data for interim analyses. Additional details will be described in the DMC charter.

9.4.1.2 Primary Analysis

The primary analysis will occur after all subjects have completed the week 12 visit or have early terminated. The primary objective of the primary analysis is to evaluate the effect of efavaleukin alfa on induction of clinical remission. All secondary objectives will also be evaluated at the time of the primary analysis.

Data will be subject to ongoing checks for integrity, completeness and accuracy in accordance with the Data Management Plan with the expectation that outstanding data issues are resolved ahead of the lock to the extent possible. The data supporting the primary analysis will be locked to prevent further changes.

9.4.1.3 Final Analysis

Final analysis activities will commence upon achieving the end of study as described in Section 4.4. The final analysis will include analysis of efficacy and safety data collected during the exploratory long-term treatment period.

Data will be subject to ongoing checks for integrity, completeness and accuracy in accordance with the Data Management Plan with the expectation that all outstanding data issues are resolved ahead of the final lock.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

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.

Unless specified otherwise, efficacy analyses will be summarized by randomized treatment group; and safety analyses will be summarized by actual treatment received.

Nominal p-values will be reported for the primary and secondary efficacy endpoints, with no adjustment for multiplicity.

9.4.2.2 Efficacy Analyses

Endpoint/ Estimand	Statistical Analysis Methods
Primary	Logistic regression will be performed to test the difference in clinical remission rates between each efavaleukin alfa dose and placebo (Ge et al, 2011). The stratification factors as captured in IRT will be included as covariates. The estimate of the risk difference between each efavaleukin alfa dose and placebo, the corresponding 2-sided 95% Wald confidence interval, and the p-value obtained from the logistic regression model will be provided. Missing primary endpoint data will be imputed using nonresponder imputation.
Secondary	Clinical response, endoscopic remission, and combined endoscopic and histologic remission will be analyzed using the same methods as the primary estimand. Change from baseline in histologic score at week 12 will be analyzed

	using an ANCOVA model with the stratification factors as capture in IRT as covariates.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2.3 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, vital signs.

9.4.2.3.1 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.

9.4.2.3.2 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics over time by each treatment group. Shifts in grades of safety laboratory values between baseline to the worst on-study value will be presented.

9.4.2.3.3 Vital Signs

The analyses of vital signs will include summary statistics over time by treatment group.

9.4.2.3.4 Physical Measurements

The analyses of physical measurements will include summary statistics over time by each treatment group.

9.4.2.3.5 Electrocardiogram

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

9.4.2.3.6 Antibody Formation

The incidence and percentage of subjects who develop anti-efavaleukin alfa antibodies and antibodies to IL-2 (binding and if positive, neutralizing) at any time will be tabulated by actual treatment received.

9.4.2.3.7 Exposure to Investigational Product

Summary statistics will be provided for the total number of doses administered of investigational product exposure by treatment.

9.4.2.3.8 Exposure to Concomitant Medication

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

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASA	aminosalicylates
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CFR	U.S. Code of Federal Regulations
cGvHD	chronic graft versus host disease
C_{max}	maximum observed concentration
COVID-19	Corona virus-19
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ET	early termination
ePRO	electronic patient reported outcome
EQ-5D-5L	EuroQol-5-Dimension 5 levels
eSAE	electronic serious adverse event
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GvHD	graft versus host disease
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCAb	hepatitis C antibody
HIV	human immunodeficiency virus
hsCRP	high sensitivity C-reactive protein
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IBG	Independent Biostatistics Group

ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL-2	interleukin-2
INR	international normalized ratio
IQR	inter-quartile range
IRB	Institutional Review Board
IRT	interactive response technology
IV	Intravaneous(ly)
JAK	Janus kinase
NCT	National Clinical Trials
NK	natural killer
PCR	Polymerase chain reaction
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
Placebo nonresponder	A subject randomized to placebo who has not achieved clinical response by week 12
Placebo responder	A subject randomized to placebo who achieves clinical response at week 12
PPD	purified protein derivative
PRO	patient reported outcome
[redacted]	
QTL	quality tolerance limit
[redacted]	
RA	rheumatoid arthritis
SC	subcutaneous(ly)
SLE	Systemic lupus erythematosus
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	total bilirubin
TNF	tumor necrosis factor
Treg	regulatory T cells
UC	ulcerative colitis
[redacted]	
ULN	upper limit of normal

VAS	visual analogue scale

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the central laboratory unless indicated as local laboratory. 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.

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

Table 11-1. Analyte Listing

Central Laboratory: Chemistry	Central Laboratory: Hematology	Central Laboratory: Urinalysis	Other Labs
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Adjusted calcium Magnesium Phosphorus Glucose BUN or Urea Total bilirubin Direct bilirubin ALP LDH AST (SGOT) ALT (SGPT) GGT Creatinine hsCRP[a] CK	RBC Hemoglobin Hematocrit MCV MCH MCHC RDW Reticulocytes Platelets WBC Differential • Bands/stabs • Eosinophils • Basophils • Lymphocytes • Monocytes • Total neutrophils • Segmented neutrophils	Protein/creatinine ratio Specific gravity pH Blood Protein Glucose Bilirubin WBC RBC Epithelial cells Bacteria Casts Crystals Central Laboratory: Coagulation PT/INR aPTT	<u>Central Laboratory</u>: Serum pregnancy FSH Quantiferon®-TB (may be performed locally) Hep B surface antigen Hep B surface antibody Hep B core antibody Hep C antibody Hep B viral DNA PCR Hep C viral RNA PCR HIV antibody Fecal calprotectin[a] Fecal lactoferrin[a] Stool *C difficile* toxin & enteric pathogens Histopathology mucosal biopsy[a] Anti-drug antibodies PK samples Biomarker development sample Biomarker mucosal biopsy Lymphocyte subset[a] PGx samples <u>Local Laboratory</u>: Urine Pregnancy PPD or T-spot

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatinine kinase; FSH = follicle stimulating hormone; GGT = gamma glutamyl transferase; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; hsCRP = high sensitivity C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PCR = polymerase chain reaction; PGx = pharmacogenetic; PPD = purified protein derivative; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count

[a] To be kept blinded after randomization and until the study is unblinded.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. Refer to Section 8.4.3 for a list of assessments that could unblind the study.

If the subject is being followed for possible drug induced liver injury (DILI), the following analytes 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, Immunoglobulin G, 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

Data Monitoring Committee(s)

The Data Monitoring Committee (DMC) is an independent, multidisciplinary group consisting of clinicians and biostatisticians that collectively have experience in the management of subjects with inflammatory disease including moderately to severely active ulcerative colitis (UC) and, in the conduct, and monitoring of randomized studies. The DMC will include at least 2 clinicians and 1 biostatistician. An Independent Biostatistics Group (IBG) will perform the interim analyses and provide the interim report to an independent DMC. The first 2 DMC meetings will occur after the first 20 subjects randomized have had the opportunity to complete the [redacted] and week 12 visits. Thereafter the DMC will plan to meet approximately every 3 months until Amgen is unblinded at the primary analysis. After Amgen is unblinded, the DMC will plan to meet every 6 months. Ad hoc meetings can be scheduled as needed. The DMC will also review all available safety and efficacy data for interim analyses (see Section 9.4.1.1 for time points). 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 IBG 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 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 sites. 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.

During the course of the study, if new information becomes available that alters the benefit-risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the IRB/IEC, and regulatory authorities, as appropriate.

The investigator will be responsible for the following:

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

Recruitment Procedures

Site staff will identify potential subjects from their existing patient population or may seek referral patients through existing professional networks or other community sources such as 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 their 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 their 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 their 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 authorized 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.

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

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

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 35 days from the previous informed consent form signature date.

The informed consent form will contain a separate section that addresses the use of remaining mandatory samples for optional 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 Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

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 their 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 Sponsor's systems. The Sponsor 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 Sponsor 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 Sponsor 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.

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 Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

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

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

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

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

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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

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

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

Quality tolerance limit (QTL) parameters 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 he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment or certain demographic information, such as gender, race, and ethnicity).

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

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

- Subject files containing completed electronic CRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study 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.

Remote Source Data Review and Verification

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those patients who participate in the trial and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorized access, access rights should be revoked once rSDR/V tasks have been completed for the trial. The EMR system should have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication.

Study and Site Closure

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

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by 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 statistical analysis plan (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 intentional overdose of either study treatment or a concomitant medication. Intentional overdose will be reported as an adverse event/serious adverse event when it is taken with possible suicidal/self-harming intent. Such intentional overdoses are to be reported regardless of sequelae. Accidental/unintentional overdose will be captured as a medication error. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:

Results in death (fatal)

Immediately life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires in-patient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other medically important serious event

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

the other outcomes listed in the above definition. These events are typically to be considered serious.

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

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).
- The investigator must assign the following 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 noninvestigational product(s)/auxiliary medicinal product(s), 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 Event electronic CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contract research organization (CRO) in lieu of completion of the Event eCRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to 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), noninvestigational product(s)/auxiliary medicinal product(s) , 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 he/she has 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.

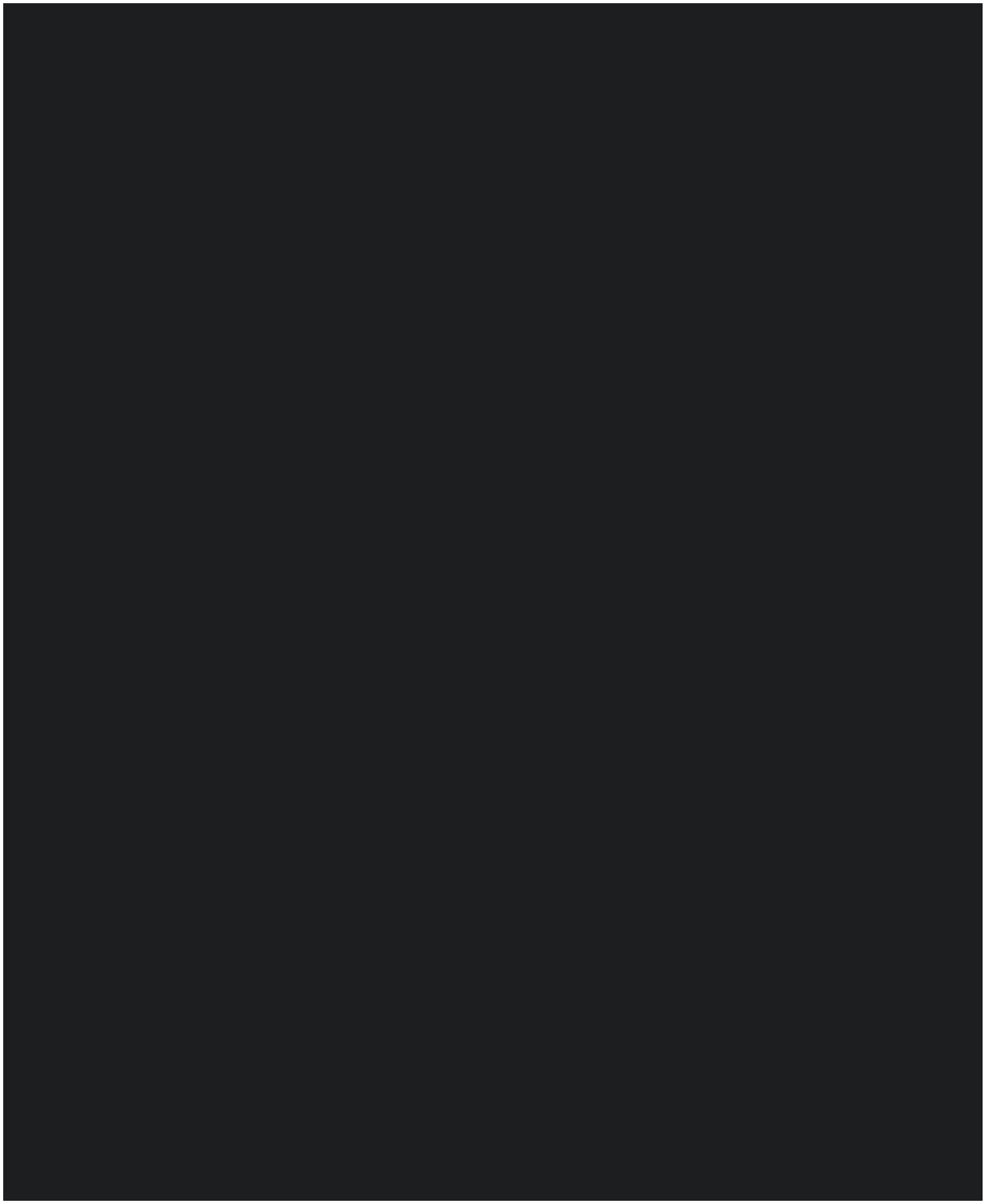
Follow-up of Adverse Event and Serious Adverse Event

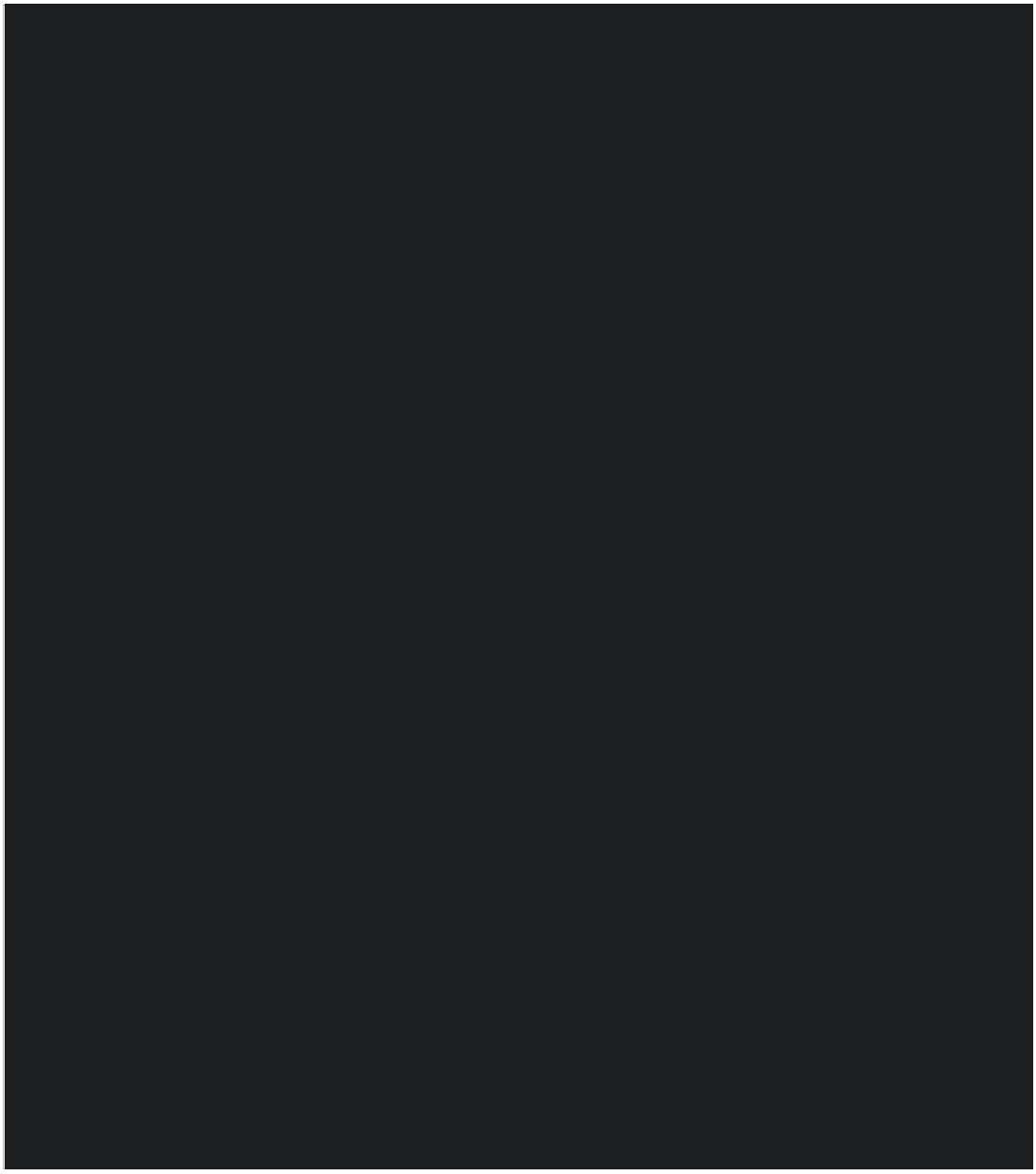
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional 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 post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event 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 electronic data capture (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 [redacted]) 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 [redacted]
- 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.





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.

Male and female subjects of childbearing potential should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant or father a child 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 post-menopausal 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 one FSH measurement is required.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) (except in Japan)
- 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

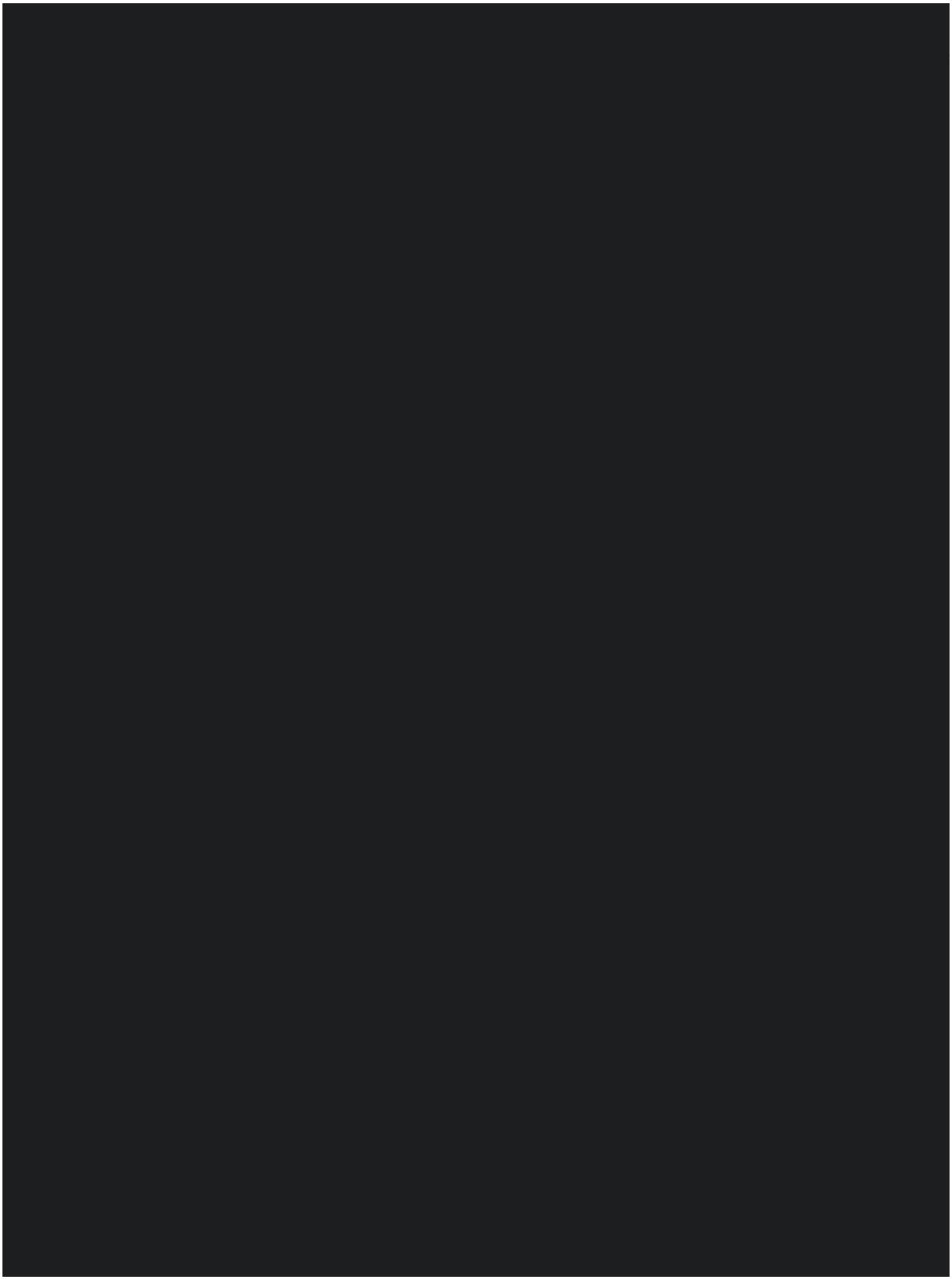
- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s) through 6 weeks after last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Form (see [redacted] 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 investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s) 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 post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in 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).

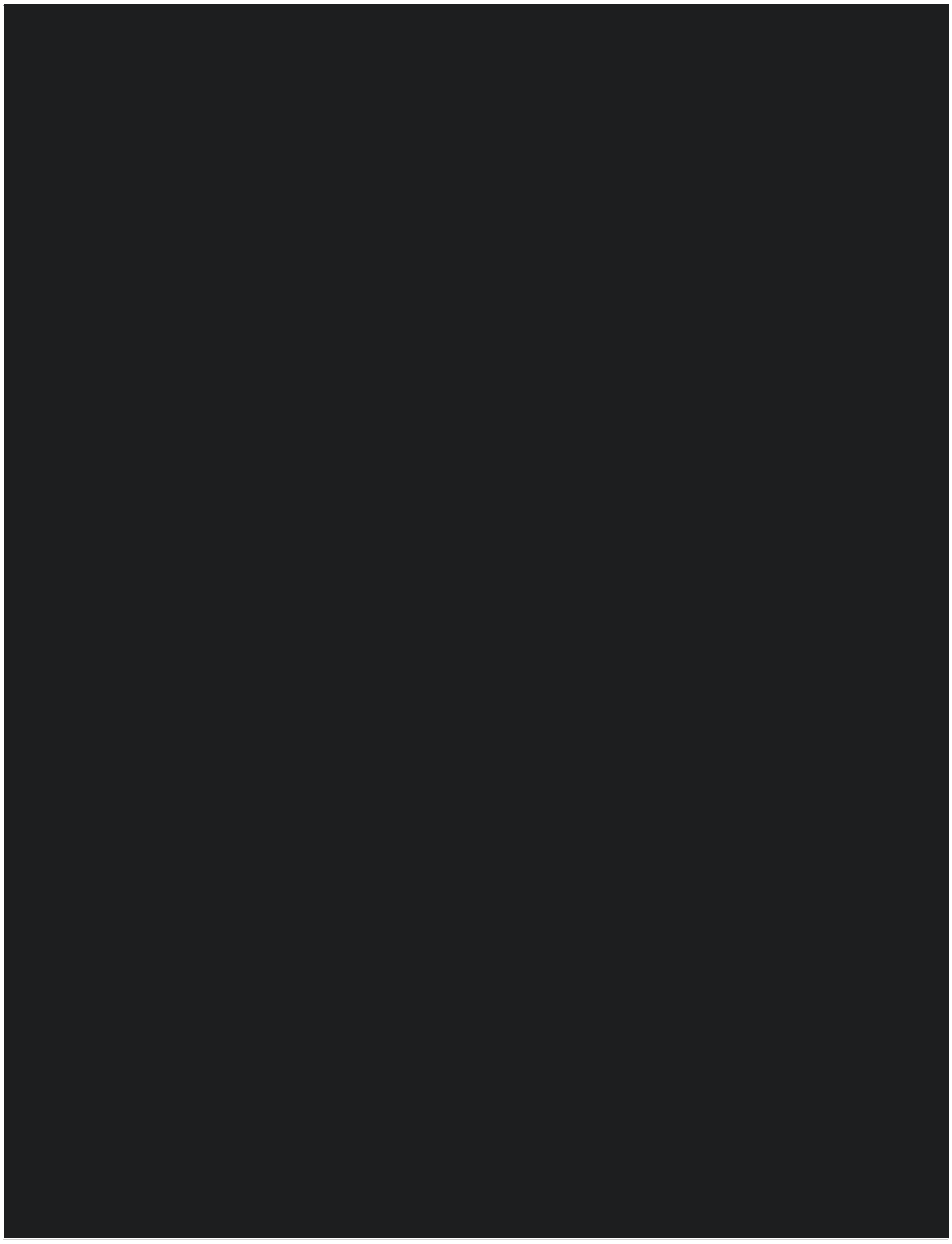
Male Subjects with Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 6 weeks after discontinuing investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s), the information will be recorded on the Pregnancy Notification Form. The form (see [redacted]) 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 investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) 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 exclusion criterion 230.
- 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 investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s) through 6 weeks after discontinuing investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s).





11.6 Appendix 6. Sample Storage and Destruction

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

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the inflammatory conditions, the dose response and/or prediction of response to 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, 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 and tissue 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)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	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 within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)

- The appropriate Case Report Form (CRF) (eg, 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 pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

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

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding eCRFs.

11.8 Appendix 8. Prohibited Medications

This section outlines medications that are prohibited during the treatment phase of the study, including windows for prohibited medications prior to the screening endoscopy, if applicable.

Drug Class	Medication Restrictions
Anti-TNF antibodies (eg, infliximab, adalimumab, golimumab)	Discontinue at least 8 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently
Anti-integrin antibodies (eg, vedolizumab)	Discontinue at least 8 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently
IL-12/23 antagonist (eg, ustekinumab)	Discontinue at least 8 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently
JAK inhibitors (eg, tofacitinib)	Discontinue at least 4 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently
S1P modulators (eg, ozanimod)	Discontinue at least 4 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently
Any other commercially approved biologic agent or targeted small molecule	Discontinue at least 8 weeks prior to screening endoscopy or 5 half-lives prior to screening endoscopy, whichever is longer, and prohibited unless the subject has stopped investigational product permanently
Immunomodulatory medications oral cyclosporine, intravenous cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, or thalidomide	Discontinue at least 4 weeks prior to screening endoscopy and prohibited throughout duration of study
Any investigational biologic therapy	Discontinue at least 8 weeks prior to screening endoscopy or 5 half-lives prior to screening endoscopy, whichever is longer, and prohibited throughout duration of study
Apheresis (eg, Adacolumn® apheresis)	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study

T cell depleting agents (eg, antithymocyte globulin, Campath).	Patients with exposure within 12 months prior to screening not eligible to be enrolled.
Recombinant IL-2 (eg, Proleukin®).	Patients with any previous exposure not eligible to be enrolled.
Corticosteroid enemas, corticosteroid suppositories, a course of IV corticosteroids or intramuscular corticosteroids, or oral budesonide standard formulation (not oral budesonide MMX)	Discontinue at least 2 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently
5-ASA enemas or 5-ASA suppositories	Discontinue at least 2 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently
Live vaccines	Last vaccination (if any) given at least 5 weeks prior to screening. Live vaccines are prohibited throughout the treatment period and for up to 6 weeks after the last dose of investigational product in the study.
Any other investigational therapies or device	Prohibited throughout duration of study.

Abbreviations: 5-ASA = 5-aminosalicyclic acid; IL-2 = interleukin-2; IL-12/23 = interleukin 12/23; IV = intravenous; JAK = Janus Kinase; TNF = tumor necrosis factor; UC = ulcerative colitis.

11.9 Appendix 9. Permitted Medications

This section outlines medications that are permitted during the treatment phase of the study, along with guidance for dose stabilization, if applicable.

Drug Class	Dose Stabilization Guidance
Immunomodulators (eg, 6-MP, AZA, or methotrexate)	Stable dose for ≥ 12 weeks prior to screening endoscopy. Doses should remain stable throughout study unless in the investigator's clinical judgment these require discontinuation or dose reduction because of toxicity or other medical necessity; even if the toxicity resolves, the therapy must not be restarted.
Oral 5-ASA compounds (eg, sulfasalazine, mesalamine)	Stable dose for ≥ 2 weeks prior to screening endoscopy. Doses should remain stable throughout the induction period. Stable doses are encouraged during the long-term treatment period.
Oral corticosteroids including budesonide (MMX) or beclomethasone dipropionate (gastro-resistant prolonged-release tablet)	Stable dose for ≥ 2 weeks prior to screening endoscopy. For subjects in clinical response or clinical remission (as assessed at week 12), who are receiving oral corticosteroids upon entry into the long-term treatment period, the investigator must begin tapering the daily dose of corticosteroids at the week 12 visit as described in Section 6.7.2.2.3.
Antidiarrheals	May continue during study with stable doses encouraged.
Non-live vaccines	Allowed during the study.

Abbreviations: 5-ASA = 5-aminosalicyclic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine

11.10 Appendix 10. Mayo Scoring System for the Assessment of Ulcerative Colitis Activity

Stool Frequency Subscore	**Score**
Normal number of stools for subject	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools than normal	3
Rectal Bleeding Subscore	**Score**
No blood seen	0
Streaks of blood stool less than half of the time	1
Obvious blood (more than just streaks) or streaks of blood with stool most of the time	2
Blood alone passed	3
Endoscopic Subscore	**Score**
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe disease (spontaneous bleeding, ulceration)	3
Physician's Global Assessment	**Score**
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3

The total Mayo score is a composite index of 4 items (stool frequency, rectal bleeding, endoscopy findings, and physician's global assessment) with each item graded semi-quantitatively on a score of 0 to 3 for a maximal total score of 12. Scores range from 0 to 12 points. The Mayo Daily Symptom Diary will be used to record stool frequency and rectal bleeding.

The modified Mayo score is the Mayo score without the physician's global assessment subscore and ranges from 0 to 9 points. The modified Mayo score will be used to assess primary and secondary efficacy endpoints. The partial Mayo score is the total Mayo score without the endoscopy subscore and ranges from 0 to 9 points.

The rectal bleeding and stool frequency subscores will be derived from the last 3 days of data entered within the last 7 days prior to the visit, or within 7 days prior to initiation of bowel preparations for visits which include an endoscopy. The average score over the 3 days will be calculated using standard rounding rules.

11.11 Appendix 11. Country-specific Requirements

This appendix provides language for country-specific regulatory requirements and other procedures to follow in the execution of the global study in these countries.

The summary of changes outlined below specify requirements for sites and subjects participating in the European Union. The country specific requirements for Japan will be outlined in a separate country specific supplement.

Table 11-4. EU Member States (Austria, Czech Republic, Italy, Poland, Germany, Hungary, Denmark, Finland, and Romania) Summary of Changes

Protocol Section	Text in Protocol	Text For European Countries
Section 4.1, Overall Design		Add:
	This phase 2 dose-finding study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week induction study of efavaleukin alfa in subjects with moderately to severely active UC who have failed at least 1 of the following: conventional therapy (eg, immunomodulators, corticosteroids), biologic therapy, or targeted small molecule (eg, JAK inhibitors). This study will be used to establish the efavaleukin alfa induction dose and maintenance dose/dosing regimens for continued development. Subjects who complete the 12-week induction period will have the option to be treated in an exploratory long-term treatment period for up to 40 additional weeks if in the opinion of the investigator they may benefit from continued treatment. The primary analysis will occur after all subjects have completed the week 12 visit or have early terminated. All primary and secondary objectives will be evaluated at the primary analysis. The objectives and endpoints for the study are defined in Section 3. The overall study design is described by a study schema in	This phase 2 dose-finding study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week induction study of efavaleukin alfa in subjects with moderately to severely active UC who have failed at least 1 of the following: conventional therapy (eg, immunomodulators, corticosteroids), biologic therapy, or targeted small molecule (eg, JAK inhibitors). This study will be used to establish the efavaleukin alfa induction dose and maintenance dose/dosing regimens for continued development (dosing decisions for further efavaleukin alfa development will not be based on one clinical efficacy endpoint alone but will include a comprehensive evaluation of all accumulated data, in particular safety and clinical pharmacology). Subjects who complete the 12-week induction period will have the option to be treated in an exploratory long-term treatment period for up to 40 additional weeks if in the opinion of the investigator they may benefit from continued treatment. The primary analysis will occur after all subjects have completed the week 12 visit or have early terminated. All primary and secondary objectives will be evaluated at the primary

Protocol Section	Text in Protocol	Text For European Countries
	Section Study Schema 1.2 (Figure 1-1).	analysis. The objectives and endpoints for the study are defined in Section 3. The overall study design is described by a study schema in Section Study Schema 1.2 (Figure 1-1).

Protocol Section	Text in Protocol	Text For European Countries
Section 4.3.2, Justification for Placebo	Not applicable	Add: 4.3.2 Justification for Placebo It is important to have a placebo arm in order to evaluate both safety and efficacy of efavaleukin alfa, an investigational product in subjects with moderately to severely active UC. Also, the inclusion of a placebo control arm is consistent with the principles outlined in International Council for Harmonization (ICH) E10 (Note for guidance on choice of control group in clinical trials). In addition, appropriate measures are in place for the safe medical supervision of subjects, and subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.
Section 5.2, Exclusion Criteria, Disease Related, Criterion 202	Replace: Criterion 202 Disease limited to the rectum (ie, within 15 cm of the anal verge).	With: Criterion 202 Disease limited to the rectum. The investigator will need to assess each individual subject to determine if disease is limited to the rectum and appropriately exclude such subjects.
Section 11.3, Appendix 3. Study Governance Considerations, Publication Policy, Paragraph 4	Not applicable	Add: Information on this study (2021-002537-41) and its results will be posted on the European Web site at www.clinicaltrialsregister.eu or on the European Union (EU) Clinical Trials Information System (CTIS), if applicable, no later than one year after the trial has ended.

Protocol Section	Text in Protocol	Text For European Countries
Section 11.5, Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information, Definition of Females of Childbearing Potential, Paragraph 4	Replace: A postmenopausal female is defined as: • A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR • A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.	With: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Table 11-5. Germany Summary of Changes

Protocol Section	Text in Protocol	Text For Germany
Section 4.1, Overall Design	This phase 2 dose-finding study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week induction study of efavaleukin alfa in subjects with moderately to severely active UC who have failed at least 1 of the following: conventional therapy (eg, immunomodulators, corticosteroids), biologic therapy, or targeted small molecule (eg, JAK inhibitors). This study will be used to establish the efavaleukin alfa induction dose and maintenance dose/dosing regimens for continued development. Subjects who complete the 12-week induction period will have the option to be treated in an exploratory long-term treatment period for up to 40 additional weeks if in the opinion of the investigator they may benefit from continued treatment. The primary analysis will occur after all subjects have completed the week 12 visit or have early terminated. All primary and secondary objectives will be evaluated at the primary analysis. The objectives and endpoints for the study are defined in Section 3. The overall study design is described by a study schema in Section Study Schema 1.2 (Figure 1-1).	Add: This phase 2 dose-finding study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week induction study of efavaleukin alfa in subjects with moderately to severely active UC who have failed at least 1 of the following: conventional therapy (eg, immunomodulators, corticosteroids), biologic therapy, or targeted small molecule (eg, JAK inhibitors). This study will be used to establish the efavaleukin alfa induction dose and maintenance dose/dosing regimens for continued development (dosing decisions for further efavaleukin alfa development will not be based on one clinical efficacy endpoint alone but will include a comprehensive evaluation of all accumulated data, in particular safety and clinical pharmacology). Subjects who complete the 12-week induction period will have the option to be treated in an exploratory long-term treatment period for up to 40 additional weeks if in the opinion of the investigator they may benefit from continued treatment. The primary analysis will occur after all subjects have completed the week 12 visit or have early terminated. All primary and secondary objectives will be evaluated at the primary analysis. The objectives and endpoints for the study are defined in Section 3. The overall study design is described by a study schema in Section Study Schema 1.2 (Figure 1-1).

Protocol Section	Text in Protocol	Text For Germany
Section 4.3.2, Justification for Placebo	Not applicable	Add: 4.3.2 Justification for Placebo It is important to have a placebo arm in order to evaluate both safety and efficacy of efavaleukin alfa, an investigational therapy in subjects with moderately to severely active UC. Also, the inclusion of a placebo control arm is consistent with the principles outlined in International Council for Harmonization (ICH) E10 (Note for guidance on choice of control group in clinical trials). In addition, appropriate measures are in place for the safe medical supervision of subjects, and subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Protocol Section	Text in Protocol	Text For Germany
Section 5.2, Exclusion Criteria, Disease Related, Criterion 202	Replace: Criterion 202 Disease limited to the rectum (ie, within 15 cm of the anal verge).	With: Criterion 202 Disease limited to the rectum. The investigator will need to assess each individual subject to determine if disease is limited to the rectum and appropriately exclude such subjects.
Section 7.1, Discontinuation of Study Treatment, Paragraph 1, Line 1	Subjects (or a legally authorized 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.	Delete (Strikethrough text only): Subjects ~~(or a legally authorized 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.
Section 8.2.1, Informed Consent	All subjects or their legally authorized representative must sign and personally date the IRB/IEC and Amgen approved informed consent before any study-specific procedures are performed.	Delete (Strikethrough text only): All subjects ~~or their legally authorized representative~~ must sign and personally date the IRB/IEC and Amgen approved informed consent before any study-specific procedures are performed.
Section 11.3, Appendix 3. Study Governance Considerations, Informed Consent Process, Paragraphs 2, 3, 6, and 8	The investigator or his/her delegated representative will explain to the subject, or their 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.	Delete (Strikethrough text only): The investigator or his/her delegated representative will explain to the subject~~, or their 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.

Protocol Section	Text in Protocol	Text For Germany
Section 11.3, Appendix 3. Study Governance Considerations, Informed Consent Process, Paragraphs 2, 3, 6, and 8 (continued)	(continued) 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.	Delete (Strikethrough text only): (continued) 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 acquisition of informed consent and the subject's agreement or refusal of their 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 authorized 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.	The acquisition of informed consent and the subject's agreement or refusal of their 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 authorized 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.
	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.	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.~~

Protocol Section	Text in Protocol	Text For Germany
Section 11.3, Appendix 3. Study Governance Considerations, Publication Policy, Paragraph 4	Not applicable	Add: Information on this study (2021-002537-41) and its results will be posted on the European Web site at www.clinicaltrialsregister.eu or on the EU CTIS, if applicable, no later than one year after the trial has ended.
Section 11.5, Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information, Definition of Females of Childbearing Potential, Paragraph 4	Replace: A postmenopausal female is defined as: • A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR • A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.	With: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Table 11-6. France Summary of Changes

Protocol Section	Text in Protocol	Text for France
Section 5.1, Inclusion Criteria, criterion 108	Not Applicable	Add: 108 Subject affiliated to a social security scheme
Section 5.2, Exclusion Criteria, Other Exclusions, criterion 238 (new)	Not Applicable	Add: 238 Subjects falling under the vulnerable population (fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, adult subjects under legal protection measures [judicial protection or guardianship measures] or others who may be considered vulnerable) unless the subjects are illiterate or visually impaired.

Superseding Amendment 4

Protocol Title: A Phase 2, Dose-finding, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Amgen Protocol Number 20170104

EudraCT Number 2021-002537-41

NCT Number: Not Applicable

Amendment Date: 21 August 2024

Rationale:

This protocol is being amended to:

- To add the EU-CT number in response to EU requirements.

Amendment 4

Protocol Title: A Phase 2, Dose-finding, Randomized, Double blind, Placebo controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Amgen Protocol Number 20170104

EudraCT Number 2021-002537-41

NCT Number: Not Applicable

Amendment Date: 17 July 2024

Rationale:

This protocol is being amended to:

- Adjust number of subjects to 240
- Modify statistical considerations to match the new number of subjects
- Align language with newer protocol template

Amendment 3

Protocol Title: A Phase 2, Dose-finding, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Amgen Protocol Number Efavaleukin Alfa 20170104

EudraCT Number: 2021-002537-41

Amendment Date: 04 May 2023

Rationale:

This protocol is being amended to incorporate the following changes into the protocol:

- Updated overall design text to include an approximate number of subjects allowed to receive a biologic or targeted small molecule therapy and added a language to clarify that screening may be closed for subjects who are naïve to biologic or targeted small molecule therapy.
- Inclusion criteria was updated to remove the 20 years age requirement as the Taiwan civil code was amended and the adult age was changed from 20 to 18 years.
- Inclusion criteria 104 was updated to align with regulatory guidance for clinical trials in population with moderately to severely active Ulcerative Colitis.
- Exclusion criteria was updated to clarify that subjects will be excluded if they receive live vaccines 5 weeks prior to screening, or plan to receive live vaccines during the treatment period and up to 6 weeks after the last dose of investigational product.
- Exclusion criteria was updated to clarify that subjects will be excluded if they have any active infection for which anti-infectives were indicated within 2 weeks (instead of 4 weeks) prior to screening.
- Included a new exclusion criterion to restrict female subjects to donate eggs during the study and also for 6 weeks after receiving the last dose of IP.

- Updated the excluded treatments, medical devices, and/or procedures during study period list to differentiate medications that are prohibited during the study and medications which are prohibited unless the subject has stopped investigational product permanently.
- Updated screening and enrollment requirement to specify that a subject must be randomized within a maximum of 35 days after the eligible screening endoscopy, including any rescreening period.
- A clarification was provided that if eligible screening assessments from previous screening periods may be used if the assessment was performed within 35 days prior to randomization.
- Included calculation for Mayo scores.
- Removed specification that hepatitis B DNA virus test details are not required for subjects with only HBsAg positive with everything else negative and history of vaccination and infection.
- Added Mayo Scoring System for the Assessment of Ulcerative Colitis Activity to the appendix.
- Included EEA country specific supplement within the protocol to specify changes that only apply to subjects in the EEA.
- Administrative, typographical, formatting, numbering, and abbreviation changes were made throughout the protocol.

Superseded Amendment 2

Protocol Title: A Phase 2, Dose-finding, Randomized, Double blind, Placebo controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Amgen Protocol Number efavaleukin alfa 20170104

Amendment Date:	09 August 2022
Superseded Amendment Date:	22 August 2022

Amendment Rationale:

The rationale for this protocol amendment is:

- To add a third interim analysis (Section 9.4)
- To add information on subject participation in the long-term extension (LTE) study (20210210) (Schedule of Assessments, Sections 4.1.2, and 8.1.4)
- To clarify study procedures at the early termination and safety follow-up visits (Section 4.4, 8.1.4)
- To clarify language regarding endoscopy assessments to specify that colonoscopy can be performed instead of rectosigmoidoscopy when clinically indicated (Section 8.3.1). In addition, “rectosigmoidoscopy” was changed to “endoscopy” throughout the document.
- To update prohibited and permitted concomitant medications (Section 5.1, 5.2, and 6.7)
- To update the dose justification section with recent data (Section 4.3.1)
- To incorporate changes for the European Union Clinical Trials Regulation (EU CTR) (Sections 1.1, 6.1, and 8.5.4)

- To consolidate the pharmacodynamics section and move it to a subsection of the biomarkers section. Also, the biomarker discovery section was removed to reduce confusion (Section 8.8)
- To reduce the frequency of pregnancy testing (Section 1.3)
- To update safety reporting language (Section 8.5.4.1)
- To clarify population definitions for the statistical methods (Section 9.3)
- To update the DMC meeting schedule (Sections 1.1, 4.1, 9.4.1, and 11.3)
- Administrative and editorial updates.

Superseded Amendment Rationale:

- To update benefit/risk information with recent data (Section 2.3).

Amendment 2

Protocol Title: A Phase 2, Dose-finding, Randomized, Double blind, Placebo controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Amgen Protocol Number efavaleukin alfa 20170104

Amendment Date: 09 August 2022

Amendment Rationale:

The rationale for this protocol amendment is:

- To add a third interim analysis (Section 9.4)
- To add information on subject participation in the long-term extension (LTE) study (20210210) (Schedule of Assessments, Sections 4.1.2, and 8.1.4)
- To clarify study procedures at the early termination and safety follow-up visits (Section 4.4, 8.1.4)
- To clarify language regarding endoscopy assessments to specify that colonoscopy can be performed instead of rectosigmoidoscopy when clinically indicated (Section 8.3.1). In addition, “rectosigmoidoscopy” was changed to “endoscopy” throughout the document.
- To update prohibited and permitted concomitant medications (Section 5.1, 5.2, and 6.7)
- To update the dose justification section with recent data (Section 4.3.1)
- To incorporate changes for the European Union Clinical Trials Regulation (EU CTR) (Sections 1.1, 6.1, and 8.5.4)
- To consolidate the pharmacodynamics section and move it to a subsection of the biomarkers section. Also, the biomarker discovery section was removed to reduce confusion (Section 8.8)
- To reduce the frequency of pregnancy testing (Section 1.3)

- To update safety reporting language (Section 8.5.4.1)
- To clarify population definitions for the statistical methods (Section 9.3)
- To update the DMC meeting schedule (Sections 1.1, 4.1, 9.4.1, and 11.3)
- Administrative and editorial updates.

Superseded Amendment 1

Protocol Title: A Phase 2, Dose-finding, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Amgen Protocol Number efavaleukin alfa 20170104

Amendment Date:	4 August 2021
Superseded Amendment Date:	11 August 2021

Amendment Rationale:

- To add hematology and chemistry laboratory assessments at week 2 of the induction period in the schedule of activities (Table 1-2)
- To add inclusion criteria age for subjects in Taiwan (Section 5.1)
- To add requirement for alternative therapy to reasons for early removal from protocol-required investigational product(s) (Section 7.1)
- To clarify language around inadequate response and disease worsening regarding subject discontinuation (Section 7.1)
- Administrative and editorial updates.

Superseded Amendment Rationale:

- To change additional pregnancy testing from monthly to [redacted] (Section 1.3 and Section 8.4.4.6)
- To add the unblinding of treatment assignment will be performed via IRT (Section 6.4.2.1)

Amendment 1

Protocol Title: A Phase 2, Dose-finding, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Amgen Protocol Number efavaleukin alfa 20170104

Amendment Date: 4 August 2021

Rationale:

The rationale for this protocol amendment is:

- To add hematology and chemistry laboratory assessments at week 2 of the induction period in the schedule of activities (Table 1-2)
- To add inclusion criteria age for subjects in Taiwan (Section 5.1)
- To add requirement for alternative therapy to reasons for early removal from protocol-required investigational product(s) (Section 7.1)
- To clarify language around inadequate response and disease worsening regarding subject discontinuation (Section 7.1)
- Administrative and editorial updates.

Approval Signatures

Document Name: Protocol Amendment efavaleukin alfa 20170104 superseding 4

Document Description: Protocol Amendment #4

Document Number: CLIN-000252783

Approval Date: 22 Aug 2024

Type of Study Protocol: Amendment

Protocol Amendment No.: superseding 4

Document Approvals	
Reason for Signing: Management	Name: [redacted] Date of Signature: 22-Aug-2024 00:13:38 GMT+0000