Title Page

Protocol Title:		A Phase 2 Long-Term Extension (LTE) Study to Evaluate The Safety and Efficacy of Efavaleukin Alfa in Subjects With Moderately to Severely Active Ulcerative Colitis
Short Protocol Title:		Long-term Safety and Efficacy of Efavaleukin Alfa in Subjects With Moderately to Severely Active Ulcerative Colitis
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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 (International Council for Harmonisation [ICH] E6).

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I have read the attached protocol entitled A Phase 2 Long-Term Extension (LTE) Study to Evaluate The Safety and Efficacy of Efavaleukin Alfa in Subjects With Moderately to Severely Active Ulcerative Colitis, dated **19 July 2024**, and agree to abide by all provisions set forth therein.

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_____
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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 2 Long-Term Extension (LTE) Study to Evaluate The Safety and Efficacy of Efavaleukin Alfa in Subjects With Moderately to Severely Active Ulcerative Colitis

Short Protocol Title: Long-term Safety and Efficacy of Efavaleukin Alfa in Subjects With Moderately to Severely Active Ulcerative Colitis

Study Phase: 2

Indication: Ulcerative Colitis (UC)

Study Rationale

This phase 2 long-term extension (LTE) study will assess the long-term safety and efficacy of efavaleukin alfa in subjects with moderately to severely active UC. Eligible subjects from the phase 2 parent dose-finding study (20170104) will have the opportunity to roll over into this LTE study. 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 LTE clinical trial in subjects with UC.

Reference should be made to the latest version of the **i**nvestigator's **b**rochure for further safety data on efavaleukin alfa.

Objective(s) and Endpoint(s)/Estimand(s)

Objectives	Endpoints
Primary	
• To evaluate the long-term safety and tolerability of efavaleukin alfa in subjects with moderate to severe ulcerative colitis (UC)	• Treatment-emergent adverse events
Secondary	
• To evaluate the effect of efavaleukin alfa long-term treatment on clinical response	• Clinical response at week 52 and 104

• To evaluate the effect of efavaleukin alfa long-term treatment on clinical remission	• Clinical remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on durable clinical remission	• Durable clinical remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on endoscopic remission	• Endoscopic remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on histologic remission	• Histologic remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on corticosteroid-free remission	• Corticosteroid-free remission at week 52 and 104 in subjects receiving corticosteroids at randomization of the phase 2 parent study (Study 20170104)
• To evaluate the effect of efavaleukin alfa long-term treatment on combined endoscopic and histologic remission	• Combined endoscopic and histologic remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on symptomatic remission	• Symptomatic remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on change in histological score	• Change from baseline of Study 20170104 in histological score (Geboes) at week 52 and 104

Overall Design

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

This study is a phase 2 long-term extension (LTE) study for subjects who completed the 52-week phase 2 parent dose-finding study (Study 20170104). Subjects will enroll into the LTE in a blinded manner on the same dose they were receiving at the completion of their participation in Study 20170104. This study will evaluate the long-term safety and clinical efficacy of efavaleukin alfa in subjects entering Study 20210210 with moderately to severely active UC.

An independent Data Monitoring Committee (DMC) will oversee safety and overall conduct of the study (Section 11.3). The DMC will review LTE study data per schedule as outlined in the DMC charter.

Study Assessments and Procedures

Efficacy assessments include the modified Mayo score using locally read endoscopies and mucosal biopsies at week 52 and week 104/ET, partial Mayo scores, biomarkers (fecal calprotectin), and patient reported outcomes (PROs). Safety assessments include physical examination, collection of adverse events and serious adverse events, chemistry, hematology, urinalysis, pregnancy testing as applicable, and immunogenicity.

This study also includes pharmacodynamic (PD) and pharmacokinetic (PK) assessments. Safety and efficacy assessments will be carried out per the schedule of assessments.

Number of Subjects

Approximately **92** subjects are expected to be enrolled into the LTE study.

Summary of Subject Eligibility Criteria

This LTE study will enroll subjects who have completed the phase 2 parent dose-finding study (Study 20170104) week 52 endoscopy and continue to meet eligibility criteria as listed in Study 20170104 and who in the opinion of the investigator may benefit from continued treatment. Exclusion criteria include permanent discontinuation of investigational product during Study 20170104 for any reason, any malignancy diagnosed during Study 20170104, active infection, or subjects currently receiving treatment in another investigational device or drug study.

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].

Eligible subjects, who in the opinion of the investigator may benefit from continued treatment, will enter the LTE study in a blinded manner on the same dose they were receiving at the completion of their participation in Study 20170104:

- [redacted] µg SC [redacted]
- [redacted] µg SC [redacted]
- [redacted] µg SC [redacted]
- Placebo SC [redacted] (if subject was a Study 20170104 [redacted] placebo responder)

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

Statistical Considerations

All safety analyses will be descriptive and will include all subjects who received at least 1 dose of efavaleukin alfa in the LTE. The primary analysis of the primary endpoint will include events starting on or after first dose of investigational product in the 20210210 study.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

Efficacy endpoints will be analyzed descriptively by treatment group.

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

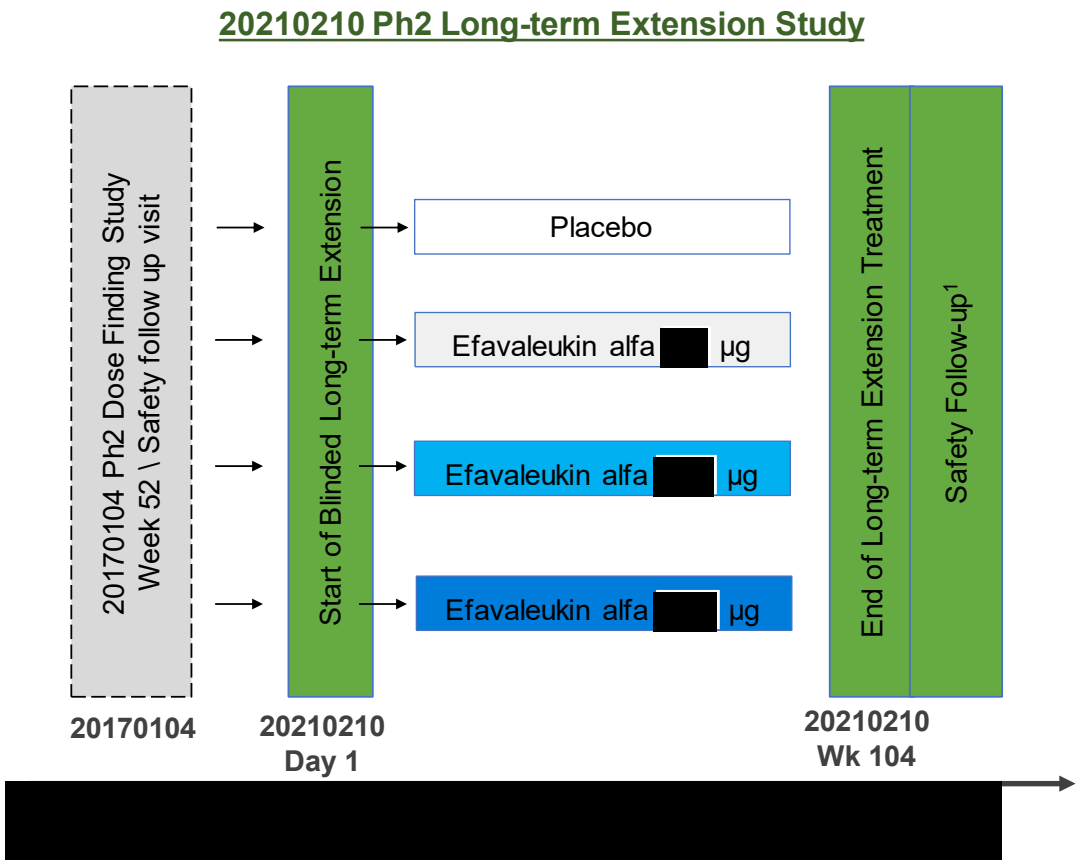
Statistical Hypotheses

No formal statistical hypotheses will be tested in this study, all analyses will be descriptive.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



Wk = week

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities – Treatment Period

	Day 1[a]	[redacted]	W52	[redacted]	Week 104/ ET
STUDY DAY +/- VISIT WINDOW		± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5	± 5	± 5 ± 5 ± 5	± 5
GENERAL AND SAFETY ASSESSMENTS					
Informed Consent	X				
Physical Examination			X		X
Height			X		X
Weight[b]			X		X
Vital Signs[c]		X X X X X X X X X X X X X X	X	X X X	X
ECG			X	X	X
Onstudy UC Related Hospitalizations/Surgeries	----------	X ----------			
Adverse Events/Serious Adverse Events[d]	----------	X ----------			
Concomitant Therapies Review	----------	X ----------			
LABORATORY ASSESSMENTS[e]					
Urine Pregnancy Test[f]	X	X X X X X X X X X X X	X	X X	X
Chemistry/Hematology		X X X X X			X
Urinalysis		X X X X X			X
Fecal Calprotectin		X	X		X
PHARMACOKINETIC ASSESSMENTS					
Pharmacokinetic Blood Sample		X	X	X	X
IMMUNOGENICITY ASSESSMENTS					
Anti-efavaleukin alfa antibody		X	X	X	X
BIOMARKER ASSESSMENTS[g]					
Biomarker Development Sample		X X X X X	X		X
Lymphocyte Subset			X		X
Biomarker Mucosal Biopsy Sample			X		X
EFFICACY ASSESSMENTS					
Partial Mayo Score Review		X X X X X X X X X X X	X	X	X
Endoscopy			X[i]		X[i]
Mucosal Biopsy (histopathology)			X		X
CLINICAL OUTCOME ASSESSMENTS					
Physician Global Assessment		X X X X X X X X X X X	X	X	X

	Day 1[a]	[redacted]	W52	[redacted]	Week 104/ ET
STUDY DAY +/- VISIT WINDOW		± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5	± 5	± 5 ± 5	± 5
Mayo Daily Symptom Diary (daily)	---------- X ----------				
[redacted]					
IBDQ		X X			X
EQ-5D-5L		X X			X
STUDY TREATMENT					
Investigational Product Administration[i]	[redacted]				

ECG = electrocardiogram; EQ-5D-5L = EuroQol-5-Dimension 5 levels; IBDQ = inflammatory bowel disease questionnaire; UC = ulcerative colitis; [redacted] W = Week; EOS = End of Study; ET = Early Termination

[redacted] f investigational product for the LTE. Subjects will undergo EOS procedures for Study 20170104 (at either W52 or Safety Follow-Up Visit) and then sign a consent to participate in the LTE study before receiving investigational product. Subject should be administered the day 1 dose for the LTE study within 3 days of Study 20170104 week 52 endoscopy or on the day of Study 20170104 safety follow-up visit.

[b] Weight measured in kilograms without shoes.

[c] Prior to each investigational product administration.

[d] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.5.1.3 for additional details.

[e] Tuberculosis (TB), human immunodeficiency virus (HIV), Hepatitis B, and/or Hepatitis C testing may be performed at the discretion of the investigator if clinically indicated (eg, due to known recent exposure).

[f] For women of childbearing potential only: urine pregnancy test is to be performed before investigational product administration on day 1 only if day 1 dosing does not occur on same day as the Study 20170104 week 52 or Safety follow-up pregnancy test. After day 1, urine pregnancy test is to be performed every 4 weeks starting with [redacted] local laboratory).

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

[redacted]

Investigational product administration at the site will continue [redacted] 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. For week 52 investigational product administration, the dosing window is up to + 3 days after the week 52 visit to allow for dosing on a separate day from the endoscopy.

[j] Locally read endoscopic subscore will be utilized.

Table 1-2. Schedule of Activities – Safety Follow-up

	Safety Follow-up (Weeks)
Week ± Visit Window	[redacted]
GENERAL AND SAFETY ASSESSMENTS	
Weight[b]	X
Vital Signs	X
Onstudy UC Related Hospitalizations/Surgeries	X
Adverse Events/ Serious Adverse Events[c]	X
Concomitant Therapies Review	X
LABORATORY ASSESSMENTS	
Urine Pregnancy Test	X
Chemistry/Hematology	X
Urinalysis	X
IMMUNOGENICITY ASSESSMENTS	
Anti-efavaleukin alfa antibody	X

UC = ulcerative colitis

[redacted]

[b] Weight measured in kilograms without shoes.
[c] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.5.1.3 for additional details.

2. Introduction

2.1 Study Rationale

This phase 2 long-term extension (LTE) study will assess the long-term safety and efficacy of efavaleukin alfa in subjects with moderately to severely active ulcerative colitis (UC). Eligible subjects from the phase 2 parent dose-finding study (20170104) will have the opportunity to roll over into this LTE study. 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.

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-tumor necrosis factor (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 and Rubin, 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 (IL-2), a multi-functional cytokine produced predominantly by activated CD4+ T cells, is a key growth factor for regulatory T cells (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 subcutaneous (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 (NK) cells, relative to low dose recombinant IL-2 (refer to efavaleukin alfa **i**nvestigator's **b**rochure 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 **i**nvestigator's **b**rochure.

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 [redacted] 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 [redacted] 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 **i**nvestigator's **b**rochure.

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

2.3.1 COVID-19

Amgen closely monitors the Coronavirus-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 206 and Section 6.1.5.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the long-term safety and tolerability of efavaleukin alfa in subjects with moderate to severe ulcerative colitis (UC)	• Treatment-emergent adverse events
Secondary	
• To evaluate the effect of efavaleukin alfa long-term treatment on clinical response	• Clinical response at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on clinical remission	• Clinical remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on durable clinical remission	• Durable clinical remission at week 52 and 104

• To evaluate the effect of efavaleukin alfa long-term treatment on endoscopic remission	• Endoscopic remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on histologic remission	• Histologic remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on corticosteroid-free remission	• Corticosteroid-free remission at week 52 and 104 in subjects receiving corticosteroids at randomization of the phase 2 parent study (Study 20170104)
• To evaluate the effect of efavaleukin alfa long-term treatment on combined endoscopic and histologic remission	• Combined endoscopic and histologic remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on symptomatic remission	• Symptomatic remission at week 52 and 104
• To evaluate the effect of efavaleukin alfa long-term treatment on change in histological score	• Change from baseline of Study 20170104 in histological score (Geboes) at week 52 and 104

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 ≥ 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
• Durable Clinical Remission	• Clinical remission at week 52 and 104 time points among subjects in clinical remission at week 12 of Study 20170104
• 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)

Exploratory	
Objectives	**Endpoints**
• To explore the effect of efavaleukin alfa long-term treatment on total Mayo score, partial Mayo score and individual subscores	• Change from baseline of Study 20170104 in total Mayo score at week 52 and 104 • Change from baseline of Study 20170104 in partial Mayo score at week 52 and 104 • Change from baseline of Study 20170104 in each individual Mayo subscore at each scheduled assessment
• To explore the effect of efavaleukin alfa long-term treatment on symptomatic and endoscopic remission without concomitant corticosteroid use	• Corticosteroid-free symptomatic remission at week 52 and 104 in subjects receiving corticosteroids at randomization of Study 20170104 • Corticosteroid-free endoscopic remission at week 52 and 104 in subjects receiving corticosteroids at randomization of Study 20170104
• To explore the effect of efavaleukin alfa long-term treatment on calprotectin levels in fecal samples	• Change from baseline of Study 20170104 in fecal calprotectin at week 52 and 104
• To explore the effect of efavaleukin alfa long-term treatment on immunogenicity	• Anti-efavaleukin alfa antibodies and crossreactivity with IL-2 • Anti-efavaleukin alfa and anti-IL-2 neutralizing antibodies
[redacted]	

[redacted]

• To explore the effect of efavaleukin alfa long-term treatment on functioning and health-related quality of life	• Change from baseline of Study 20170104 in social function and emotional function scores as measured by the IBDQ at each scheduled assessment • Change from baseline of Study 20170104 in IBDQ overall score at each scheduled assessment
• To explore the effect of efavaleukin alfa long-term treatment on changes in quality of life	• Change from baseline of Study 20170104 in VAS scores as measured by the EQ-5D-5L at each scheduled assessment
• To explore the effect of efavaleukin alfa long-term treatment on colectomy or UC-related complications	• Colectomy for UC or UC-related complications
• To explore the effect of efavaleukin alfa long-term treatment on UC-related hospitalizations	• Incidence and duration of UC-related hospitalizations

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

4. Study Design

4.1 Overall Design

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

This study is a phase 2 LTE study for subjects who completed the 52-week phase 2 parent dose-finding study (Study 20170104). Subjects will enroll into the LTE in a blinded manner on the same dose they were receiving at the completion of their participation in Study 20170104. This study will evaluate the long-term safety and

clinical efficacy of efavaleukin alfa in subjects entering Study 20210210 with moderately to severely active UC.

Participants in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 9.2.

4.2 Patient Input into the Study Design

Patient input was obtained for design of Study 20170104. No additional patient input was obtained for the design of this LTE Study.

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

In Study 20170104, subjects with moderately to severely active UC are randomized to receive one of the following induction doses: [redacted] µg [redacted] [redacted] µg [redacted] [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 in Study 20170104, [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 increases in other IL-2–responsive cells, although interpretation is limited due to small subject numbers. As of 26 April 2022, no deaths, life threatening, AMG 592 related 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] and [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 2 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 no observed adverse effect level (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** ha**ve** completed [redacted]. The total study duration for an individual subject may be up to [redacted] weeks. This includes up to 104 weeks of long-term treatment, and a safety follow-up [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, antibody testing), as applicable.

5. Study Population

Eligibility criteria will be evaluated during the enrollment period.

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 the following criteria apply:

101 Subject has provided informed consent **before** initiation of any study specific activities/procedures.

102 Subject has completed the week 52 endoscopy in the phase 2 parent dose-finding study (20170104) and who in the opinion of the investigator may benefit from continued treatment.

5.2 Exclusion Criteria

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

201 Permanent discontinuation of investigational product during the 52-week phase 2 dose finding study (20170104) for any reason.

Disease Related

202 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.
- 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 non-adenoma 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.

Other Medical Conditions

203 Any malignancy diagnosed during Study 20170104, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.

204 Active infection (including chronic, acute, recurrent, opportunistic infections) at the time of eligibility evaluation requiring intravenous (IV) anti-infectives or hospitalization (infections requiring oral and/or topical anti-infective[s] for > 7 days may be allowed in consultation with the Amgen physician).

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

Prior/Concomitant Therapy

206 Plan to receive a live (attenuated) vaccine during the treatment period and up to 6 weeks after the last dose of investigational product in the LTE study.

Prior/Concurrent Clinical Study Experience

207 Currently receiving treatment in another investigational device or drug study. Other investigational procedures while participating in this study are excluded.

Other Exclusions

208 Female subjects who are 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.

209 Female subjects of childbearing potential unwilling to use protocol specified method of contraception see Appendix 5 (Section 11.5) during treatment and for an additional 6 weeks after the last dose of investigational product.

210 Subject has known sensitivity to any of the products to be administered during dosing except **for** subjects who exhibited sensitivity in Study 20170104 but did not result in treatment discontinuation.

211 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.

212 Subject has a history or evidence of any other clinically significant disorder (including laboratory abnormalities), condition, or disease 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.

214. 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 **external review bodies (eg, the** institutional review board **[**IRB**]**/independent ethics committee **[**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 **external review body** approved informed consent before commencement of study-specific procedures.

All subjects who enter the study will keep the same subject identification number from Study 20170104. 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.

A subject is considered enrolled once they receive their first dose of investigational product in the LTE study. 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).

5.4 Ineligible Subjects

Ineligible subjects are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of information will be collected that includes demography, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study will not be enrolled. Refer to Section 8.1.1.

6. Study Intervention

Study intervention is defined as any investigational product(s), noninvestigational product(s)**/auxiliary medicinal product(s)**, 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 noninvestigational product(s)**/auxiliary medicinal product(s) are referred to as noninvestigational 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) 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: investigational product administration on day 1 and at week 52 has a dosing window up to + 3 days after the visit to allow for dosing on a separate day from the endoscopy.

Subjects must remain at the site for at least 30 minutes following dose administration.

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

Subjects will continue to receive the dose of investigational product (placebo or efavaleukin alfa) that they were receiving at the completion of their participation in Study 20170104:

- [redacted] µg SC [redacted]
- [redacted] µg SC [redacted]
- [redacted] µg SC [redacted]
- Placebo SC [redacted] (if subject was a Study 20170104 week 12 placebo responder)

6.1.2 Medical Devices

No investigational medical devices will be used in the study.

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

Non-Amgen noninvestigational 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 Noninvestigational Product(s)/Auxiliary Medicinal Product(s)

There are no **noninvestigational product(s)/auxiliary medicinal product(s)** in this study.

Concomitant medications are described in Section 6.7.

6.1.4 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, **noninvestigational product(s)/auxiliary medicinal product(s)** provisioned and/or repackaged/modified by Amgen:

Any product complaint(s) associated with efavaleukin alfa, **noninvestigational product(s)/auxiliary medicinal product(s)** supplied by Amgen are to be reported.

6.1.5 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 devices
- 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, anti-TNFs [infliximab, adalimumab, or golimumab]) or biosimilars to these agents
- Targeted small molecules (eg, S1P modulators or JAK inhibitors)
- Intravenous 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 or Placebo

No individual 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 6.1.5 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**, noninvestigational product(s)/auxiliary medicinal product(s)** 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

Subjects were randomized into treatment groups upon enrollment into Study 20170104. Subjects will remain in the treatment group that they concluded with in Study 20170104 during the blinded portion of this LTE study.

6.4.2 Blinding

The blinded LTE period of this study is a double-blind study. Unblinding information consists of subject treatment assignments, including contents of investigational product boxes (eg, manufacturing lot number), and potentially unblinding data (PUBD) which has the potential to indicate treatment assignment for an individual subject.

Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below until unblinding occurs based on the Study 20170104 primary analysis and the open label period begins.

6.4.2.1 Site Personnel Access to Unblinding Information

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 **Study** 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 **Study** 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 interactive response technology (IRT).

Unblinding information will not be accessible by investigative sites or subjects before the completion of the final analysis except for an emergency unblinding.

6.4.2.2 Access to Unblinding Information by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information is not to be distributed to the study team, investigators or subjects prior to the study being formally unblinded except as specified (eg, Section 6.4.2.1).

6.5 Treatment Compliance

When subjects are dosed 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 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 6.1.5 (summarized in Section 11.8). Refer to Section 6.7.1 for permitted medications specifically for the treatment of UC (summarized in Section 11.9).

Concomitant therapies **that the subject receives** are to be collected from enrollment 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. Any concomitant therapies ongoing at the end of Study 20170104 will be transferred by Amgen into the LTE concomitant medications CRF.

6.7.1 Permitted Medications for the Treatment of UC

The following concomitant medications for the treatment of UC are permitted:

- Oral and topical (rectal) 5-ASA treatment; stable doses of these medications are encouraged.
- Oral corticosteroids are permitted under the guidelines described in Section 6.7.1.2.
- Topical (rectal) corticosteroid enemas/suppositories; stable doses of these medications are encouraged.
- Azathioprine, 6-mercaptopurine, or methotrexate; stable doses of these medications are encouraged. See Section 6.7.1.1.

- Antibiotics.
- Antidiarrheals for control of chronic diarrhea.
- Probiotics (eg, Culturelle, S. boulardii).

6.7.1.1 Immunomodulators

Subjects who were receiving the following immunomodulators for UC at the time of entry into the LTE and do not experience disease worsening must keep their prescribed dosage stable through completion of the 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 above-mentioned therapy must not be restarted:

- 6-mercaptopurine,
- azathioprine, or
- methotrexate.

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

6.7.1.2 Oral Corticosteroid Dosing and Tapering Regimen

The maximum dose of oral corticosteroid for the treatment of IBD that may be co-administered with efavaleukin alfa as a long-term regimen is 30 mg/day prednisone (or equivalent), 9 mg/day budesonide MMX, or 5 mg/day beclomethasone dipropionate (gastro-resistant prolonged-release tablet). Short-term use of higher doses, or corticosteroids that are required for pre-dose medication (to be given only on the day of dose administration), is acceptable. However, subjects who require consistent doses higher than 30 mg/day prednisone (or equivalent) should be withdrawn from the investigational product. Cases in which the investigator believes the subject should stay on-study must be discussed with Amgen physician.

It is strongly recommended that subjects receiving oral corticosteroids should begin an oral corticosteroid tapering regimen once they either achieve clinical response or if, in the opinion of the investigator, they have demonstrated sufficient improvement.

The 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.
- 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.

Investigators should strongly consider withdrawing subjects who require recurrent corticosteroid courses with an inability to taper.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects have the right to withdraw from investigational product**(s), noninvestigational product(s)/auxiliary medicinal product(s)**, **and/or** 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, **noninvestigational product(s)/auxiliary medicinal product(s)** device, and/or protocol procedures, or the study as a whole at any time **before** study completion for the reasons listed in Section 7.

7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized representative) can decline to continue receiving investigational product and/or **noninvestigational product(s)/auxiliary medicinal product(s)** 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 **and/**or **noninvestigational product(s)/auxiliary medicinal product(s)** and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 1-1) 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 product complaints (including device-related adverse events, as applicable) and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or **noninvestigational product(s)/auxiliary medicinal product(s)** 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 investigational product(s), **noninvestigational product(s)/auxiliary medicinal product(s) and/or** procedur**es** may include any of the following:

- decision by sponsor*****
- lost to follow-up
- death
- adverse event
- subject request
- ineligibility determined
- protocol deviation
- non-compliance
- requirement for alternative therapy
- pregnancy
- protocol-specified criteria:
    - A colectomy (partial or total) or an ostomy
    - Disease-worsening per the partial Mayo score

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

7.2 Subject Discontinuation/Withdrawal From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further **investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s),** procedures, 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 1-1) for data

to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

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

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if **they** repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether 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 (see Table 1-1 and Table 1-2).

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 Confirmation of Eligibility and Enrollment

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

Informed consent must be obtained before completing any study procedure. After the subject has signed the ICF, the site will evaluate the subject in order to assess eligibility for participation and once eligibility has been confirmed, register the subject in the IRT.

Day 1 for this LTE study and the Study 20170104 week 52 endoscopy should occur within 3 days. All efforts should be made to minimize any time gaps between Study 20170104 week 52 endoscopy and the day 1 dose in the LTE study.

In circumstances where a subject cannot receive the day 1 dose of the LTE study within 3 days following the Study 20170104 week 52 endoscopy, they must proceed into the Study 20170104 safety follow-up period for up to [redacted]. These subjects must complete the Study 20170104 safety follow-up assessments prior to entering the LTE study and must receive the day 1 dose of the LTE study on the same day as the Study 20170104 safety follow-up visit assessments (dosing should occur after assessments that day) or they will be considered ineligible for entry into the LTE study.

All eligibility criteria must be reviewed and completed to confirm that potential subjects may be enrolled.

At the day 1 visit, if the subject meets all eligibility criteria, they are assigned to the treatment regimen they were receiving at the end of Study 20170104. The subject is considered enrolled when they receive the first dose of investigational product.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1). On-study visits may be completed within ± 5 days. The date of the first dose of investigational product**/noninvestigational product(s)/auxiliary medicinal product(s)** is defined as day 1. All subsequent doses and study visits will be scheduled based on 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. The treatment period is defined as enrollment through the planned week 104 visit.

8.1.3 Safety Follow-up/End of Study

A safety follow-up will be performed [redacted] (Table 1-2). Subjects who discontinue investigational product early should follow the planned scheduled assessments for at least [redacted] after the last dose of investigational product to ensure the safety follow-up is complete.

If futility is met in the 52-week phase 2 parent dose-finding study (Study 20170104), subjects in this phase 2 LTE study will have a scheduled early termination visit and a [redacted]. The investigator will be required to determine standard of care therapy which the subject will receive after study termination.

Refer to Section 4.4 for the end of study definition

8.2 General Assessments

8.2.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the **external review body** approved informed consent before any study-specific procedures are performed.

8.2.2 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).

8.2.3 Physical Measurements

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

8.3 Efficacy Assessments

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

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 (Section 11.10) 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 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.

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 is required for all subjects at week 52 and 104/ET visits. Colonoscopy can be performed instead of rectosigmoidoscopy at week 52 and 104/ET visits for clinically indicated reasons in the judgement of the investigator and after discussion with the Amgen physician as appropriate.

Rectosigmoidoscopy (or if applicable colonoscopy) will be performed as part of the total and modified Mayo Score. The procedure can be performed by the investigator or qualified designee using the institution's standard procedure and study manual.

All rectosigmoidoscopies (or if applicable colonoscopy) will be read locally by the investigator (or designee).

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.



[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 (VAS). 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.

8.4 Safety Assessments

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

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 and Table 1-2) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Events CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as **an** 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 (Table 1-1 and Table 1-2).

Fecal calprotectin, central histology reads, antibody, PK, and lymphocyte subsets that are collected after enrollment 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

Tuberculosis testing is to be performed at the discretion of the investigator, if clinically indicated (eg, due to known recent exposure). Subjects may receive either a purified protein derivative (PPD), QuantiFERON®-TB, or T-Spot test. A chest X-ray will be performed for subjects with a positive tuberculosis (TB) 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 **by** the delegation of authority for this responsibility. Purified protein derivative 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, 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, the test will be performed locally with the test kits procured locally.

8.4.3.2 HIV Antibodies, Hepatitis B, and Hepatitis C Testing

Human immune virus (HIV), Hepatitis B, and Hepatitis C testing are to be performed at the discretion of the investigator, if clinically indicated (eg, due to known recent exposure). If the results show a negative hepatitis B surface antigen (HbsAg) and positive hepatitis B core antibody (HBcAb) quantification of hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Similarly, if the results show a positive HCAb, a quantification of serum hepatitis C virus RNA by PCR is necessary. If performed, the above-mentioned PCR test results must be negative for the subject to continue in the study. Subjects positive for HBcAb without history of prior vaccination and without detectable serum Hepatitis B viral DNA by PCR, are allowed to continue in the study, 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 **hepatitis B surface antibody**, negative HBsAg, and negative HBcAb) are allowed to continue in the study. Any subjects who required serum viral DNA (Hepatitis B virus) monitoring in Study 20170104 must continue monitoring during the LTE treatment period and up to 6 weeks after the end of treatment in the LTE.

8.4.3.3 Fecal Calprotectin, 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 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 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 may be tested at the discretion of the investigator if clinically indicated 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.

8.4.4 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent

and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

8.4.5 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.

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

8.4.5.1.1 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 enrollment through the end of study are reported using the Events CRF.

Any ongoing adverse event at the end of Study 20170104 will be transferred by Amgen into the LTE study Events CRF.

8.4.5.1.2 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 first dose of investigational product through the end of study are reported using the Events CRF.

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 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.

8.4.5.1.3 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 after the protocol-required reporting period (as defined in Section 8.4.5.1.2) is complete, these serious adverse events will be reported to Amgen immediately and no later than 24 hours **after** 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 **study** 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.

8.4.5.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to inquire 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 about adverse event occurrence.

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

8.4.5.3 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 **after investigator's** 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 CRF.

8.4.5.4 Regulatory Reporting Requirements for Safety Information

If subject is permanently withdrawn from **investigational product(s), and/or noninvestigational 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, **external review body**, and investigators.

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

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the **i**nvestigator's **b**rochure and will notify the **external review body**, 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. **T**o 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 **study**, if applicable.

8.4.5.5 Safety Monitoring Plan

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

8.4.5.6 Other Safety Findings/Special Situations (OSF/SS)

All medication errors, misuse, or abuse of the investigational product when associated with a serious adverse event must be reported to Amgen or designee immediately and no later than 24 hours of the investigator's awareness by collecting and recording the OSF/SS event on the Clinical Trial eSAE Contingency Report Form and submitting the form to Amgen Global Patient Safety or designee.

Further details and definitions regarding OSF/SS - medication errors, misuse, and abuse can be found in Section 11.4.

8.4.5.7 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 sensitive (urine) pregnancy test should be completed for females of childbearing potential before investigational product administration on day 1 only if day 1 dosing does not occur on same day as the Study 20170104 week 52 or Safety follow-up pregnancy test. After day 1, urine pregnancy testing is to be performed every 4 weeks starting with [redacted] (local laboratory).

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 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 continued on 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).

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 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 and Table 1-2) for the measurement of anti-efavaleukin alfa antibodies. Samples testing positive for anti-efavaleukin alfa antibodies 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.

8.7 Biomarkers

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

8.7.1 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). 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.

8.7.2 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).

Biomarker mucosal biopsy: Biopsy for biomarker development will be performed at the time points indicated in the Schedule of Activities (Table 1-1). 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.

8.7.3 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.

8.8 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 medical resource use 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

No formal statistical hypothesis will be tested in this study, all analyses will be descriptive.

9.2 Sample Size Determination

[redacted]

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Full Analysis Set	All enrolled subjects, analyzed by planned treatment group
Safety Analysis Set	All enrolled subjects, analyzed by actual treatment group

9.3.1 Covariates

No covariates will be considered in this study because no modeling will be conducted.

9.3.2 Subgroups

Secondary efficacy endpoints may be explored and not limited to the following subgroups:

- Stratification factors used in Study 20170104 randomization:

- Prior experience with at least 1 biologic or targeted small molecule: (yes, no)
- Corticosteroid use at randomization: (yes, no)

- Age: ($<$ 40 years, $\geq$ 40 years)
- Sex: (female, male)
- Race: (white, non-white)

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 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.

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

Statistical analyses in this LTE are descriptive in nature. No statistical inference is planned. No formal hypothesis will be tested in this study. Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given. Unless specified otherwise, the baseline value is defined as the subject's baseline value from Study 20170104. Unless specified otherwise, efficacy analyses will be summarized by planned treatment group; and safety analyses will be summarized by actual treatment received.

9.4.2.2 Efficacy Analyses

Endpoint/ Estimand	Statistical Analysis Methods
Secondary	Summary statistics will be provided for all secondary efficacy endpoints.
Exploratory	Will be described in the statistical analysis plan finalized before database lock.

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	All safety analyses will be performed using the Safety Analysis Set based on subject's actual treatment received.

9.4.2.3.2 Adverse Events

The analysis of the primary endpoint will include events starting on or after first dose of investigational product in the LTE study.

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 **noninvestigational product(s)/auxiliary medicinal product(s)** and treatment emergent adverse events will also be provided.

9.4.2.3.3 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.

9.4.2.3.4 Vital Signs

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

9.4.2.3.5 Physical Measurements

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

9.4.2.3.6 Electrocardiogram

The ECG measurements from this clinical study will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential

QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.4.2.3.7 Antibody Formation

[redacted]

9.4.2.3.8 Exposure to Investigational Product

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

9.4.2.3.9 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
ASA	aminosalicylates
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BIL	bilirubin
CFR	U.S. Code of Federal Regulations
cGvHD	chronic graft versus host disease
C_{max}	maximum observed concentration
COVID-19	Coronavirus-19
CRF	case report form
CRO	contract research organization
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
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
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCAb	hepatitis C antibody
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobin
IL-2	interleukin-2
INR	international normalized ratio

IQR	inter-quartile range
IRT	interactive response technology
IV	Intravaneous(ly)
JAK	Janus kinase
LTE	Long-term extension
NCT	National Clinical Trials
NK	natural killer
NOAEL	no observed adverse effect level
PCR	Polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
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
S1P modulator	Sphingosine-1-phosphate receptor modulator
SAP	Statistical analysis plan
SC	subcutaneous(ly)
SLE	Systemic lupus erythematosus
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). Local laboratories may be used if necessary.

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

Tuberculosis (TB), human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C, and/or coagulation testing may be performed at the discretion of the investigator if clinically indicated (eg, due to known recent exposure). 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	RBC	Protein/creatinine ratio	Central Laboratory:
Potassium	Hemoglobin	Specific gravity	Serum pregnancy
Chloride	Hematocrit	pH	FSH
Bicarbonate	MCV	Blood	Quantiferon®-TB (may be performed locally)
Total protein	MCH	Protein	Hep B surface antigen
Albumin	MCHC	Glucose	Hep B surface antibody
Calcium	RDW	Bilirubin	Hep B core antibody
Adjusted calcium	Reticulocytes	WBC	Hep C antibody
Magnesium	Platelets	RBC	Hep B viral DNA PCR
Phosphorus	WBC	Epithelial cells	Hep C viral RNA PCR
Glucose	Differential	Bacteria	HIV antibody
BUN or Urea	• Bands/stabs	Casts	Fecal calprotectin[a]
Total bilirubin	• Eosinophils	Crystals	Stool *C difficile* toxin & enteric pathogens
Direct bilirubin	• Basophils		Histopathology mucosal biopsy[a]
ALP	• Lymphocytes	Central Laboratory: Coagulation	Anti-drug antibodies
LDH	• Monocytes		PK samples[a]
AST (SGOT)	• Total neutrophils	PT/INR	Biomarker development sample
ALT (SGPT)	• Segmented neutrophils	aPTT	Biomarker mucosal biopsy
GGT			Lymphocyte subset[a]
Creatinine			
CK			Local Laboratory:
			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; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PCR = polymerase chain reaction; PK = pharmacokinetic; 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 enrollment 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, RBC Count, 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 D RNA, Hepatitis E RNA, 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; DILI = drug-induced liver injury; EDA = early antigen; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; NA = nuclear antigen; PT = prothrombin time; RBC = red blood cell; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; VCA = viral capsid antigen; 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 UC and, in the conduct, and monitoring of randomized studies. The DMC will include at least 2 clinicians and 1 biostatistician. The DMC will review all available safety and efficacy data periodically in accordance with the DMC charter. Ad hoc meetings can be scheduled as needed. The Independent Biostatistics Group (IBG) and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and Data Monitoring Group will not have any direct contact with study site personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master file 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 (ICF), **i**nvestigator's **b**rochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an **external review body** by the investigator and reviewed and approved by the **external review body**. 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 **external review body** for all protocol amendments

and changes to the informed consent document that Amgen distributes to the site. The investigator must send a copy of the approval letter from the **external review body** and amended protocol Investigator's Signature page to Amgen **before** 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 **external review body**, and regulatory authorities, as appropriate.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the **external review body** annually or more frequently in accordance with the requirements, policies, and procedures established by the **external review body**
- Obtaining annual **external review body** approval/renewal throughout the duration of the study. Copies of the investigator's reports and the **external review body** continuance of approval must be sent to Amgen
- Notifying the **external review body** 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 **external review body**, and all other applicable local regulations

Recruitment Procedures

Site staff will identify potential subjects from their existing patient population enrolled in Study 20170104. All patient facing materials must be reviewed/approved by the sponsor (Amgen Inc.) and the local **external review body**.

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at **their** site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen **Study** 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 **their** 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 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 **external review body** 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 person **who conducted** the informed consent **discussion (investigator or their delegated representative)** 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. If the subject agrees to such notification **(or it is a local requirement)**, 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.

The ICF will contain a separate **consent** 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 **external review body** 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 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.

Serious Breach

Suspected Serious Breaches must be reported to the study team or the Clinical Out-of-Hours Support Program: https://wwwext.amgen.com/science/clinical-trials/clinical-out-of-hours-support-program immediately and no later than 1 calendar day from the time of awareness.

A Serious Breach is a breach of any of the following:

- **Good Clinical Practice (GCP)**
- **the clinical trial protocol**
- **an applicable regulation**

That is likely to impact to a significant degree either of the following:

- **the safety, physical, or mental integrity and the rights of the subject**
- **the reliability and robustness of the data and the scientific value of the trial**

Publication Policy

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

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be prepared in accordance with Amgen's publications policy and submitted to Amgen for review. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly

Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work 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.

Results Reporting

Results will be reported to clinical trial registries in accordance with the applicable regulatory requirements. The final summary results will be reported following the global end of study (as defined in Section 4.4) to ensure data from all sites globally are included in the reported results.

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or 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, **external review body** review, and regulatory agency inspections and provide direct access to source data documents.

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

The sponsor or designee will perform ongoing source data verification to confirm that data entered 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 Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, **investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal products(s)** storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

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

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

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

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

Source Documents

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

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the interactive response technology (IRT) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment 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 **i**nvestigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, **i**nvestigator's **b**rochure, copies of pre-study documentation, and all correspondence to and from the **external review body** 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
- Noninvestigational product(s) **/auxiliary medicinal 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 **i**nvestigator reserve the right to terminate the **i**nvestigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the **external review body** 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 [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting 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 o**verdose 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 **on the events CRF**. **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 preexisting 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 preexisting 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.

Other Safety Findings/Special Situations: Medication Errors, Misuse, or Abuse	
All medication errors, misuse, or abuse of the investigational product when associated with a serious adverse event, the OSF/SS must be reported to Amgen or designee immediately and no later than 24 hours of the investigator's awareness by submitting the paper-based Clinical Trial eSAE Contingency Report Form.	
Definitions	**Medication Error: A medication error is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the participant (eg, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice.**
	Misuse: A misuse refers to situations where the medicinal product, combination product, or medical device is intentionally and inappropriately used not in accordance or outside what is foreseen in the protocol.
	Abuse: An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, combination product, or medical device, which is accompanied by harmful physical or psychological effects.

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 **before** first dose of investigational product, **noninvestigational product(s)/auxiliary medicinal product(s),** and/or **devices** – 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)**, – **Assessment of relatedness to** study-**required** activity and/or procedures **is only required for Serious Adverse Events** – Action taken; – 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 Events CRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, except **for** 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 assess severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on The Common Terminology Criteria for Adverse Events (CTCAE), version 5 which is available at the following location:

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

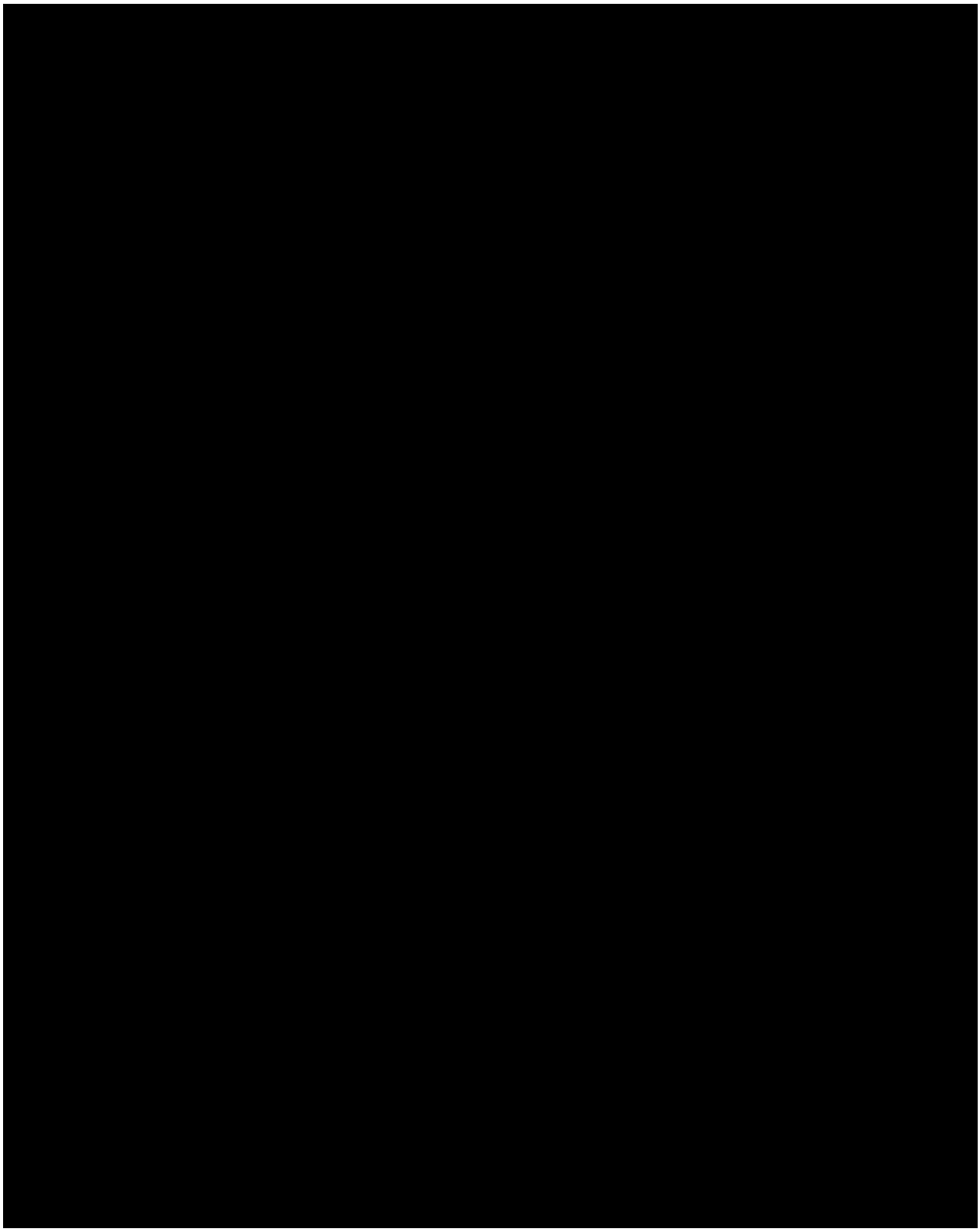
Assessment of Causality

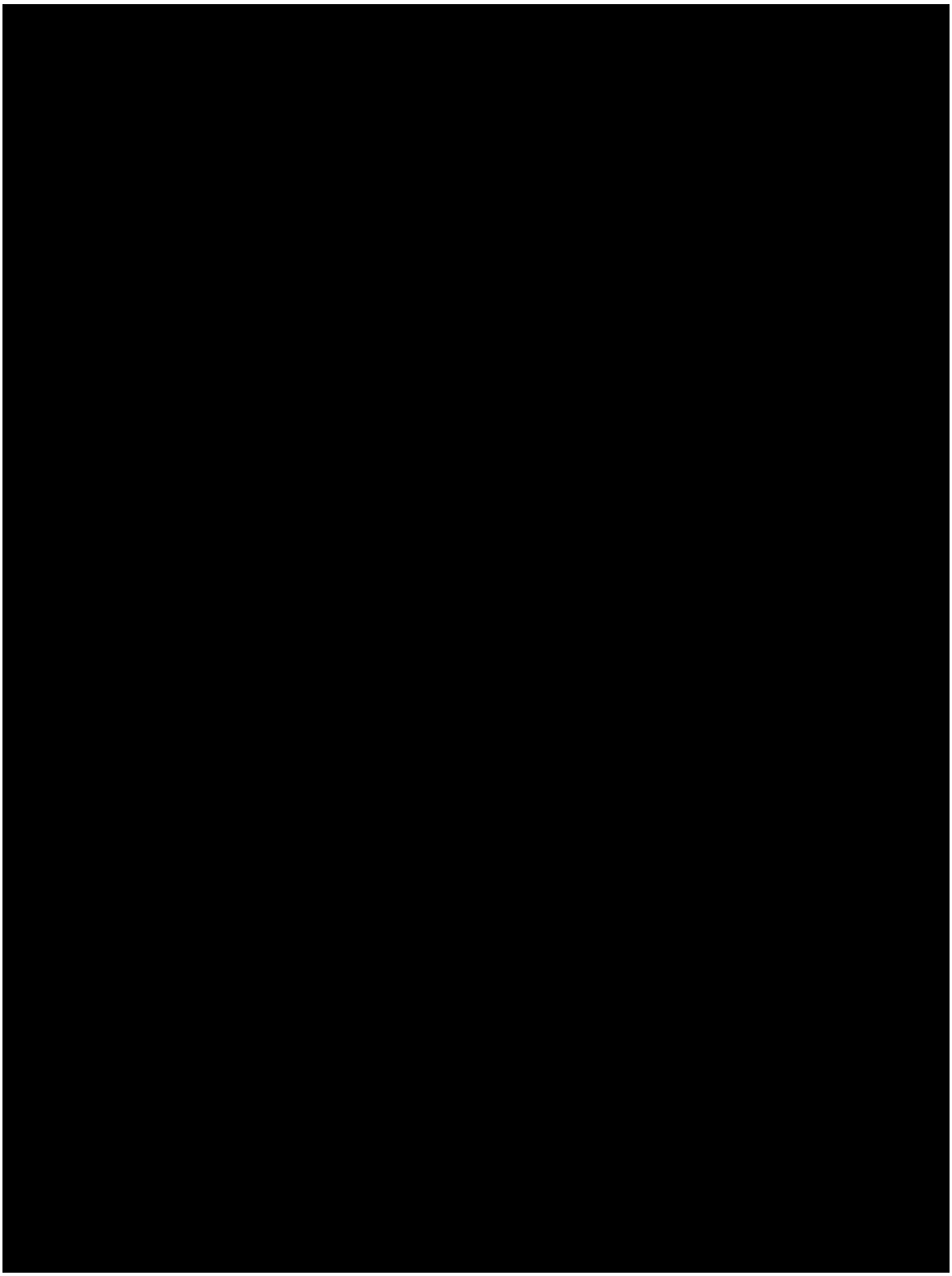
- The investigator is obligated to assess the relationship between investigational product(s) **noninvestigational product(s)/auxiliary medicinal product(s)** , device(s), and/or study-**required** activity and/or procedure(s) and each occurrence of each adverse event/serious adverse event.
- **The investigator is obligated to assess the relationship between investigational product(s) [investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), device(s), study-required activity and/or procedure(s)] and each occurrence of each 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 **i**nvestigator's brochure and/or Product Information, for marketed products, in **their** assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that **they** ha**ve** 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 assess causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change **their** 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.

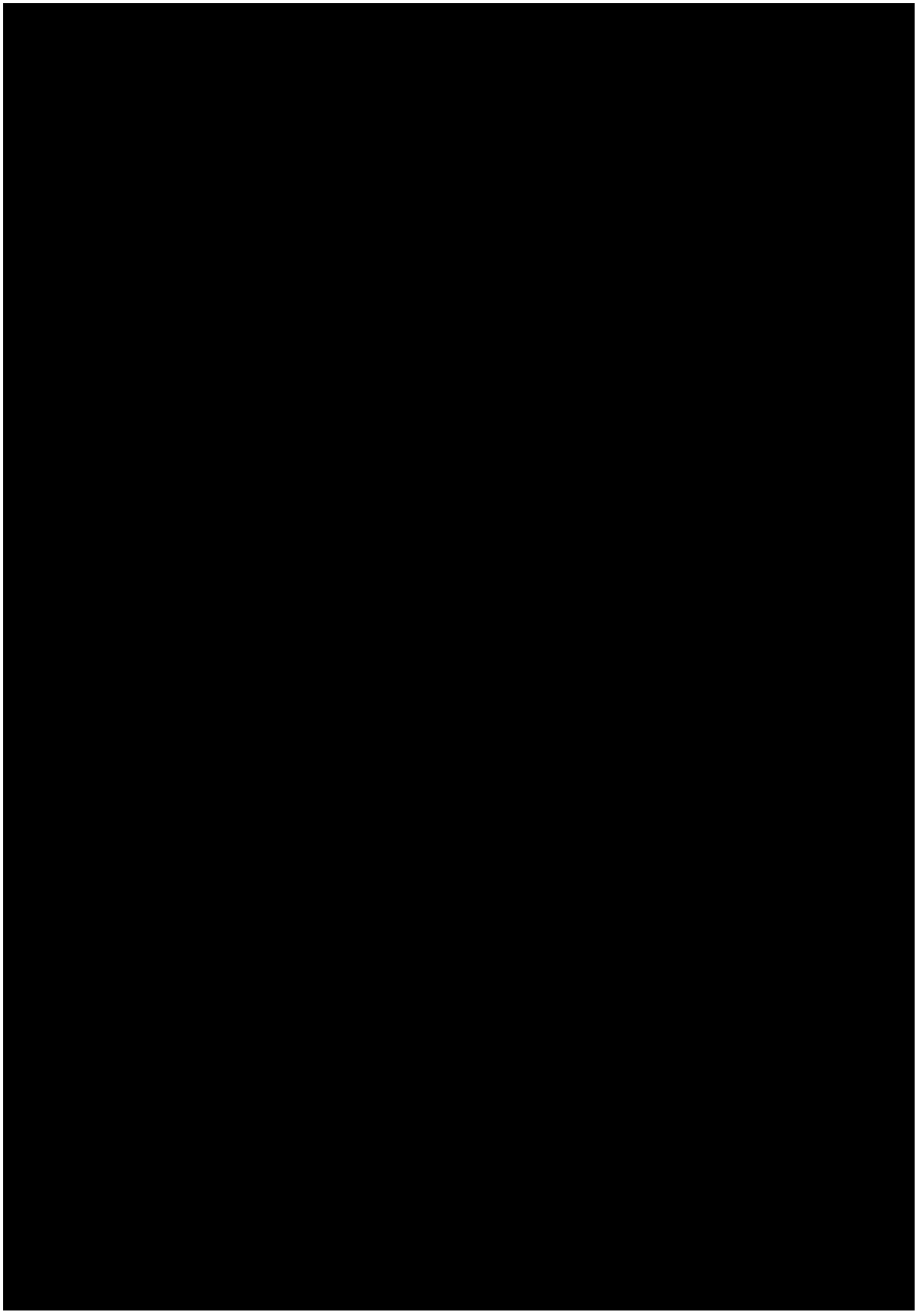
Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event 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 **investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s)** because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed Events CRF. • The investigator will submit any updated serious adverse event data to Amgen **immediately and no later than** 24 hours of receipt of the information.

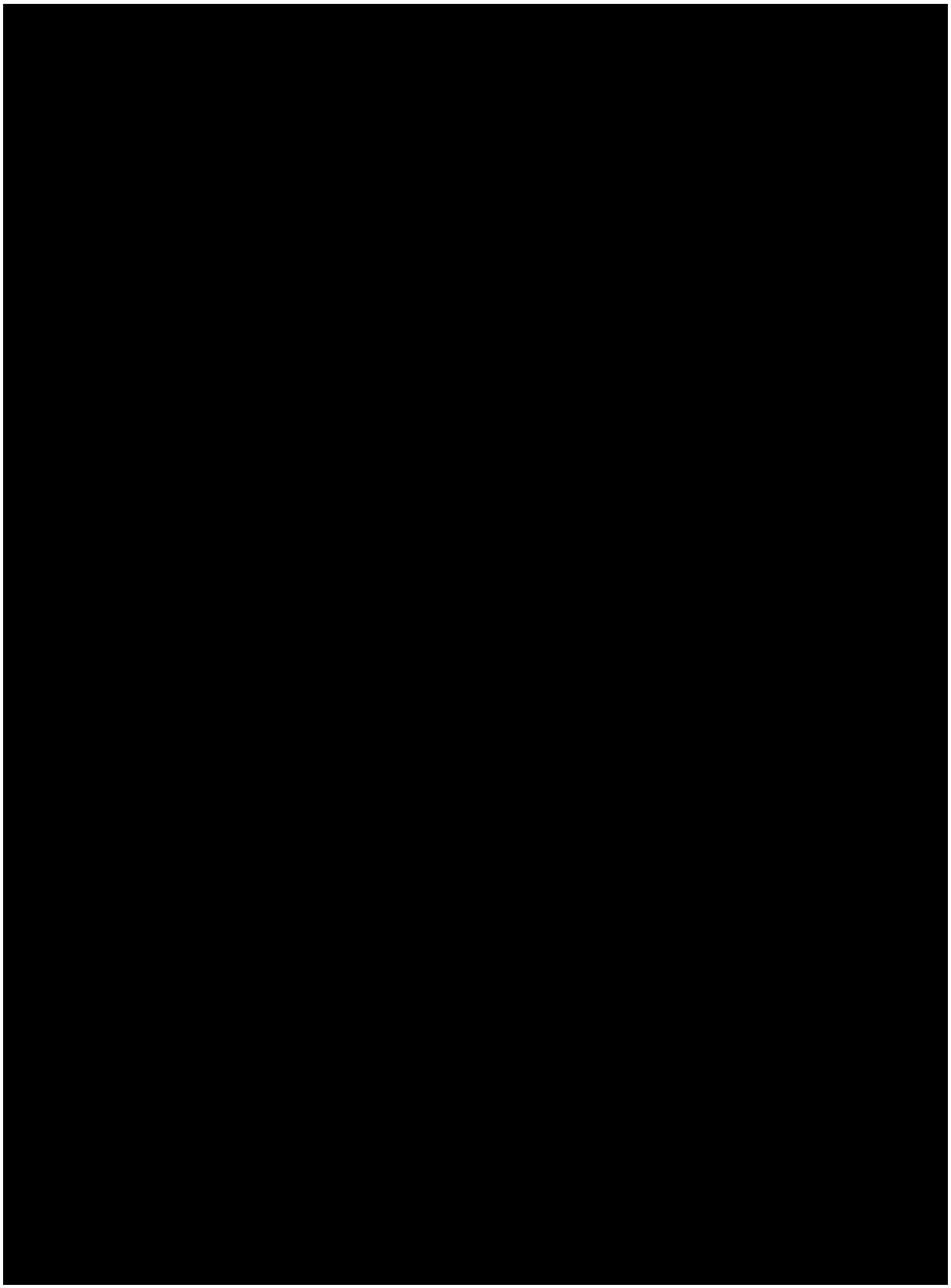
Reporting of Serious Adverse Event

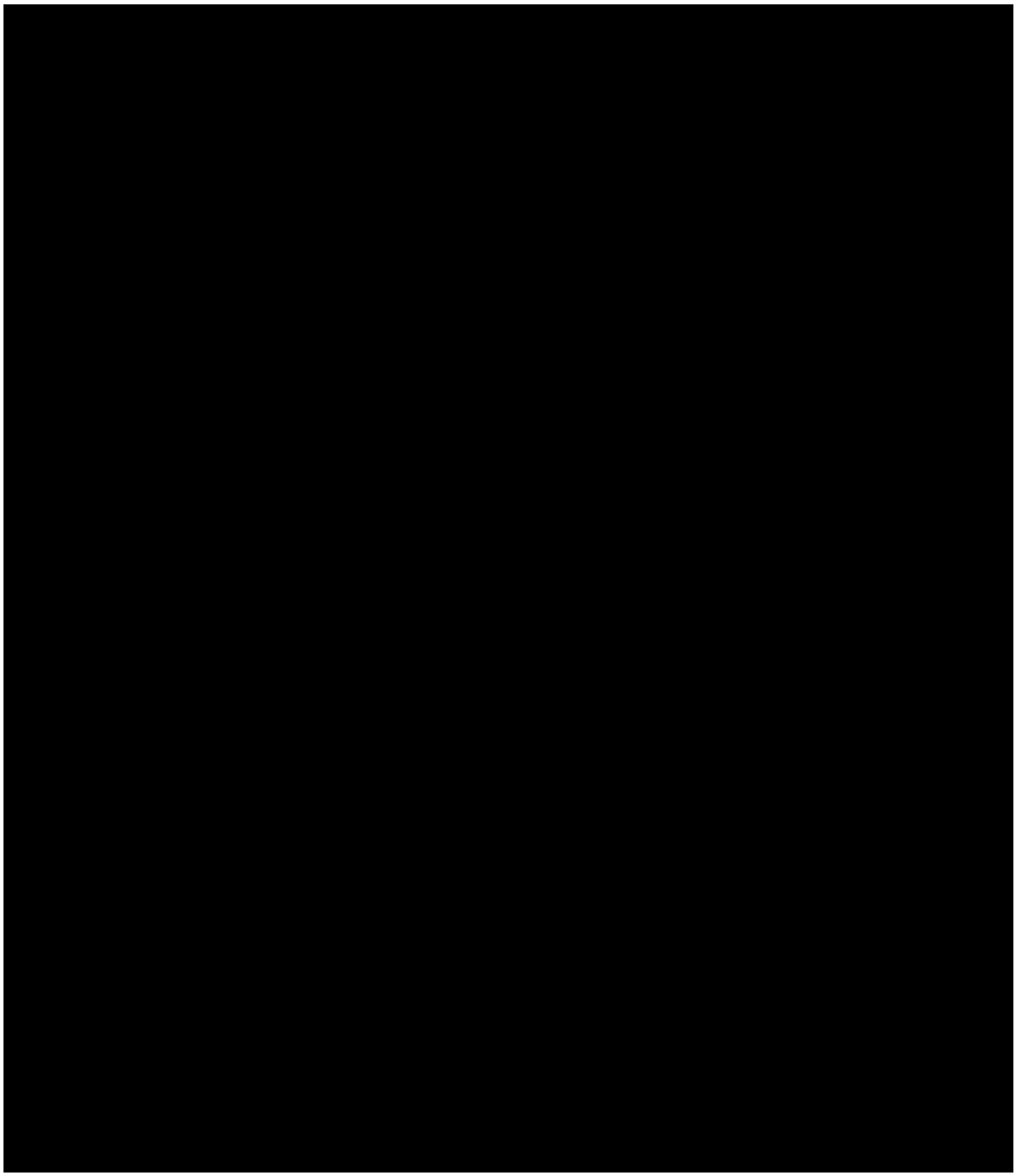
Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system. • If the EDC system is unavailable, then the site will report the information to Amgen using a paper-based Serious Adverse 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 **immediately and no later than 24 hours o**f the investigator's aware**ness** of **the** 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 an additional 6 weeks after the last dose of **investigational product**.

Definition of Females of Childbearing Potential

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

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

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

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A woman age < 55 years with no menses for at least 12 months and with a follicle stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (**if** 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 **study** 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 noninvestigational 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 noninvestigational 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 poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, **they** may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment while pregnant (see Section 7.1 for details).

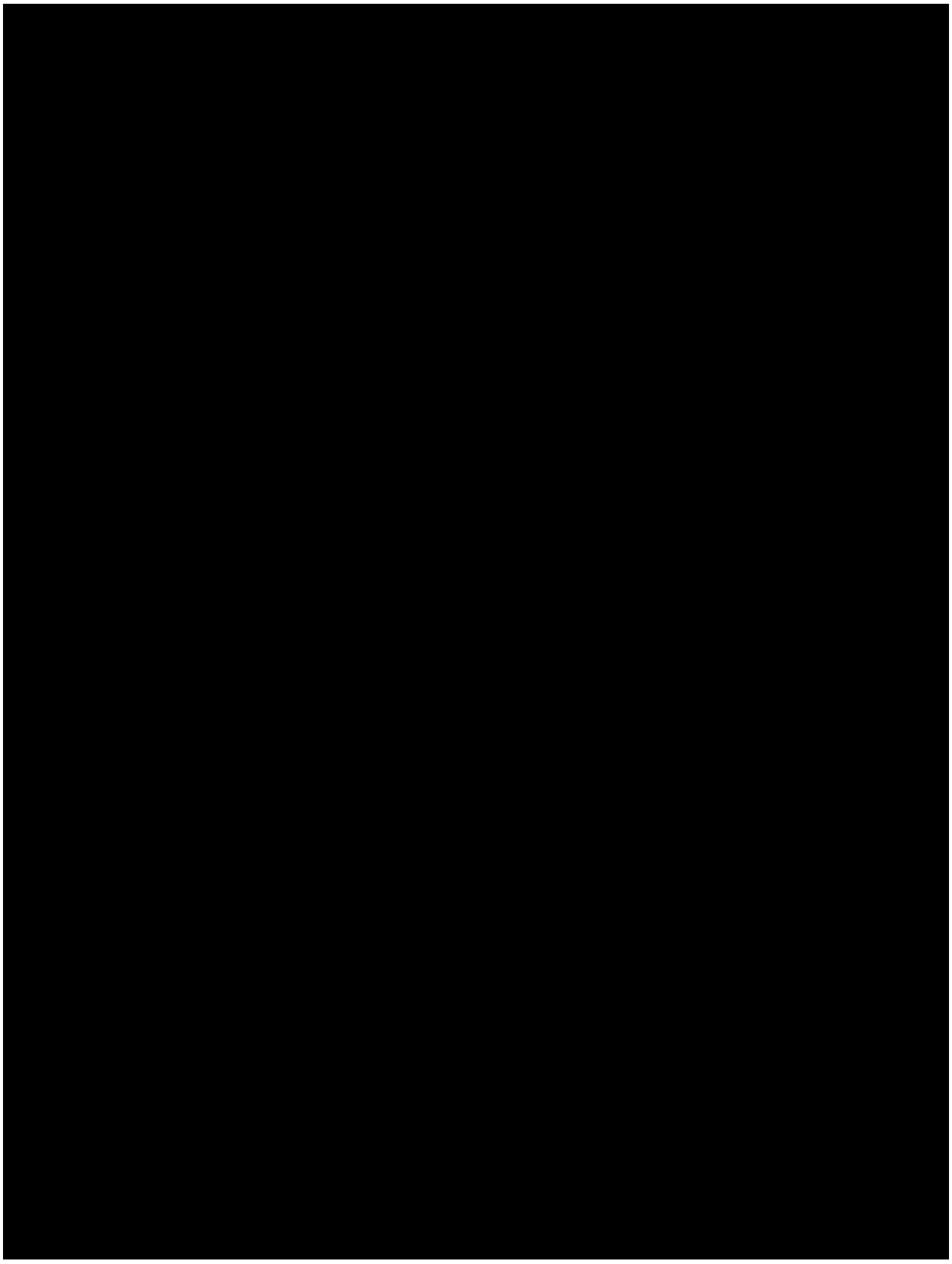
Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

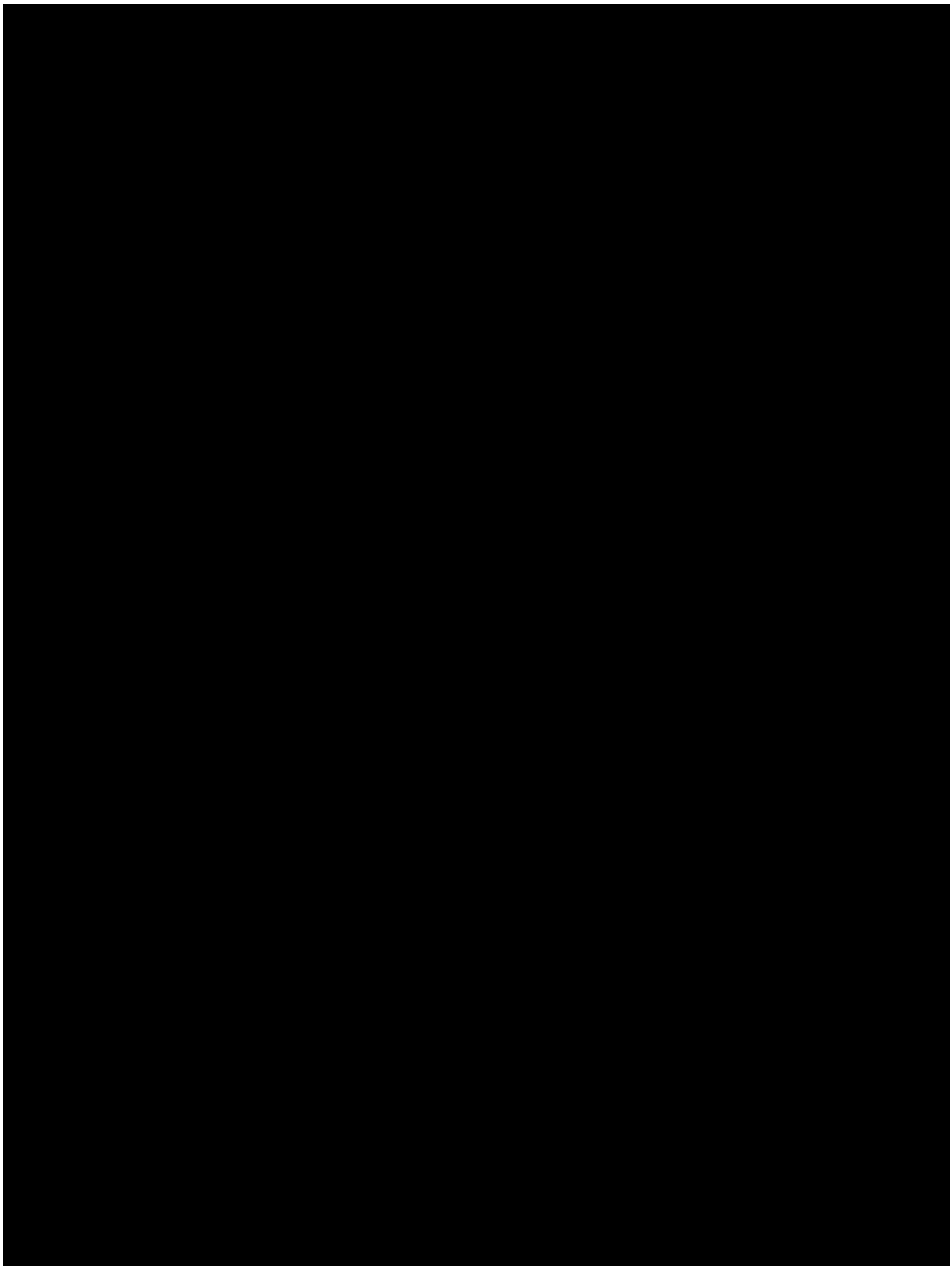
- In the event a male subject fathers a child during treatment, and for an additional 6 weeks after discontinuing **investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s)**, the information will be recorded on the Pregnancy Notification Form. The form (see [redacted] 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 208.
- 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 noninvestigational product(s)/auxiliary medicinal product(s)** through 6 weeks after discontinuing **investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s).**





11.6 Appendix 6. Sample Storage and Destruction

When permitted by local regulations 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 **before** being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

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

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, 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. **After** 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 **before** 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 **noninvestigational product(s)/auxiliary medicinal product(s)**, 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/or noninvestigational product(s)/auxiliary medicinal product(s) 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-1 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/or Noninvestigational Product(s)/Auxiliary Medicinal Product(s)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 Noninvestigational Products/Auxiliary Medicinal Products After Potential Hepatotoxicity

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

If signs or symptoms recur with rechallenge, then efavaleukin alfa is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-3) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event **immediately and no later than** 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate case report form (CRF) (eg, Events CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or **noninvestigational products/auxiliary medicinal products** 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) **and/or noninvestigational product(s)/auxiliary medicinal product(s)** 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 (PK) analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

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

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

11.8 Appendix 8. Prohibited Medications

This section outlines medications that are prohibited during the study.

Drug Class	Medication Restrictions
Commercially available biologic agents (eg, vedolizumab, ustekinumab, anti-TNFs [infliximab, adalimumab, or golimumab]) or biosimilars to these agents	Prohibited unless the subject has stopped investigational product permanently
JAK inhibitors (eg, tofacitinib)	Prohibited unless the subject has stopped investigational product permanently
S1P modulators (eg, ozanimod)	Prohibited unless the subject has stopped investigational product permanently
Any other commercially approved biologic agent or targeted small molecule	Prohibited unless the subject has stopped investigational product permanently
Immunomodulatory medications oral cyclosporine, intravenous cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, or thalidomide	Prohibited throughout duration of study
Any investigational biologic therapy	Prohibited throughout duration of study
Apheresis (eg, Adacolumn® apheresis)	Prohibited throughout duration of study
T cell depleting agents (eg, antithymocyte globulin, Campath).	Prohibited throughout duration of study
Recombinant IL-2 (eg, Proleukin).	Patients with any previous exposure **are** not eligible to be enrolled. Prohibited throughout duration of study
IV corticosteroids or intramuscular corticosteroids, or oral budesonide standard formulation (not oral budesonide MMX)	Prohibited unless the subject has stopped investigational product permanently
Live vaccines	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; 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 maximum dose and dose stabilization, if applicable.

Drug Class	Dose Stabilization Guidance
Immunomodulators (eg, 6-MP, AZA, or methotrexate)	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 and topical (rectal) 5-ASA compounds (eg, sulfasalazine, mesalamine)	Allowed during the study with stable doses encouraged.
Oral corticosteroids including budesonide (MMX) or beclomethasone dipropionate (gastro-resistant prolonged-release tablet)	The maximum doses are 30 mg/day prednisone (or equivalent), 9 mg/day budesonide MMX, or 5 mg/day beclomethasone dipropionate. Short-term use of higher doses, or corticosteroids that are required for pre-dose medication (to be given only on the day of dose administration), is acceptable. See Section 6.7.1.2 for guidance on higher doses. It is strongly recommended that subjects receiving oral corticosteroids should begin a tapering regimen (described in Section 6.7.1.2) once they either achieve clinical response or if, in the opinion of the investigator, they have demonstrated sufficient improvement.
Corticosteroids for non-UC indications: corticosteroids to treat adrenal insufficiency, or locally administered corticosteroids (eg inhaled, intranasal, intra-articular, topical)	Allowed during the study with stable doses encouraged.
Antidiarrheals	Allowed during the study with stable doses encouraged.
Antibiotics	Allowed during the study.
Probiotics (eg, Culturelle, S. boulardii)	Allowed during the study.
Non-live vaccines	Allowed during the study.
Abbreviations: 5-ASA = 5-aminosalicyclic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine. UC = ulcerative colitis.	

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.

Total and modified Mayo scores will be calculated using the data for each subscore based on the date of the endoscopy.

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.

Table 11-4. France Summary of Changes

Protocol Section	Text in Protocol	Text for France
Section 5.1, Inclusion Criteria	Not applicable	Added the following text: **103 Subject affiliated to a social security scheme**
Section 5.2, Exclusion Criteria	Not applicable	Added the following text: **213 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.**

Table 11-5. Italy Summary of Changes

Protocol Section	Text in Protocol	Text For Italy
Section 4.3.2, Justification for Placebo	Not applicable.	Add: **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. 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). Subjects enrolled, including subjects on the placebo control arm, are permitted to receive background UC therapies which include the following classes: oral corticosteroids, 5-aminosalicylates, and select conventional immunomodulators. 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.**

Table 11.5. Italy Summary of Changes

Protocol Section	Text in Protocol	Text For Italy
Section 5.1, Inclusion Criteria, criterion 102	Subject has completed the week 52 endoscopy in the phase 2 parent dose-finding study (20170104) and who in the opinion of the investigator may benefit from continued treatment.	Add: Subject has completed the week 52 endoscopy **and demonstrated clinical response at week 52 (using locally read endoscopic subscore)** in the phase 2 parent dose-finding study (20170104) and who in the opinion of the investigator may benefit from continued treatment.
Section 11.3, Appendix 3. Study Governance Considerations, Publication Policy, Paragraph 4	Not applicable.	Add: **Information on this study (2022-001686-12) and its results will be posted on the European Web site at www.clinicaltrialsregister.eu or on the European Union Clinical Trials Information System (CTIS), if applicable, no later than 1 year after the trial has ended.**

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Table 11-6. Germany Summary of Changes

Protocol Section	Text in Protocol	Text For Germany
Section 7.1, Discontinuation of Study Treatment, Paragraph 1	Subjects (or a legally authorized representative) can decline to continue receiving investigational product and/or noninvestigational product(s)/auxiliary medicinal product(s) and/or procedures at any time during the study but continue participation in the study.	Deleted the following text: Subjects ~~(or a legally authorized representative)~~ can decline to continue receiving investigational product and/or noninvestigational product(s)/auxiliary medicinal product(s) 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 external review body approved informed consent before any study-specific procedures are performed.	Deleted the following text: All subjects ~~or their legally authorized representative~~ must sign and personally date the external review body 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 their 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 procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.	Deleted the following text: The investigator or their 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 procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Table 11-6. Germany Summary of Changes

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)	Deleted the following text: (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 external review body or study site.	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 external review body 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.

Amendment # 2

Protocol Title: A Phase 2 Long-Term Extension (LTE) Study to Evaluate The Safety and Efficacy of Efavaleukin Alfa in Subjects With Moderately to Severely Active Ulcerative Colitis

Amgen Protocol Number: Efavaleukin alfa 20210210

NCT Number: NCT05672199

EU CT Number: 2023-506046-24

Amendment Date: 19 July 2024

Rationale:

This protocol amendment was performed to include the following key changes:

- Update “other protocol-required therapies” and “protocol-permitted therapies” with “noninvestigational product(s)/auxiliary medicinal product(s)” throughout the protocol as per European Union Clinical Trial Registration (EUCTR) requirements.
- Update external review bodies as a term to refer to IRBs/IECs and regulatory authorities.
- Update sample size from 140 to 92 subjects.
- Update a statement that 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 in Sections 8.4.5.1.2, 8.4.5.3, and 11.5 (Appendix 5).
- Include language related to medication errors, misuse, or abuse of the investigational product in Sections 8.4.5.7, and 11.4 (Appendix 4).
- Add language for serious breaches and study results reporting in Section 11.3 (Appendix 3).
- Updates to country-specific requirements to align with current protocol amendment in Section 11.11 (Appendix 11).

- Make other minor changes, including recent protocol template changes, updates to administrative information and abbreviations, and typographical and formatting corrections, throughout the document.

Amendment 1

Protocol Title: A Phase 2 Long-Term Extension (LTE) Study to Evaluate The Safety and Efficacy of Efavaleukin Alfa in Subjects With Moderately to Severely Active Ulcerative Colitis

Amgen Protocol Number: (Efavaleukin Alfa [AMG 592]) 20210210

NCT Number: NCT05672199

EudraCT Number/EU CT Number: 2022-001686-12/2023-506046-24

Amendment Date: 03 August 2023

Rationale:

This protocol has been amended to include corrections in the schedule of activities, clarify when a subject requiring corticosteroids should be removed from the study treatment, align with the recently amended 52-week phase 2 parent dose-finding study (Study 20170104), and consolidate 3 approved country-specific supplements for France, Italy, and Germany in the appendix. Below is a list of the changes:

Corrections and Clarifications

- Schedule of Activities-Treatment Period:
  - Added study day visit window for [redacted]
  - Added physical examination at Week 52.
  - Added weight as a separate assessment at Week 52 and Week 104/End of Treatment.
  - Removed week 24 lymphocyte subset sample.
  - Included a footnote that week 52 and 104 endoscopies were assessed locally.
- Schedule of Activities-Safety Follow-up:
  - Corrected footnotes for vital signs and adverse events.
- Added that subjects who require consistent doses higher than 30 mg/day prednisone (or equivalent) should be withdrawn from the investigational product instead of from the study.

Alignment with Study 20170104

- Clarified the study rationale to include that eligible subjects from the phase 2 parent dose-finding study (20170104) will have the opportunity to roll over into this long-term extension (LTE) study.
- Added height and weight as separate assessments in the Schedule of Activities and included this as a clarification in the Physical Measurement section of the protocol.
- Included a new exclusion criterion to restrict female subjects to donate eggs during the study and for 6 weeks after receiving the last dose of investigational product.
- Updated the excluded treatments, medical devices, and/or procedures during study period. Added a list to differentiate medications that are prohibited during the study and medications which are prohibited unless the subject has stopped investigational product permanently.
- Updated reasons for removal of a subject from the study.
- Updated language describing when a subject is considered lost to follow up to align with the protocol template language.
- Added guidance in case futility is met in the 52-week phase 2 parent dose-finding study (Study 20170104). In this case, subjects in the phase 2 long-term expansion study will have a scheduled early termination visit and a 6-week follow up visit after last dose of investigational product.
- Updated Efficacy Assessments for Mayo score (Total, Modified, and Partial) to correct language incorrectly stating that modified Mayo score would be used as part of primary efficacy assessment. The actual primary endpoint of this study is treatment-emergent adverse events which doesn't require Mayo score. The secondary efficacy endpoints on this study require Mayo scores, and definitions of the sub-scores are defined in Appendix 10.
- Updated Efficacy Assessments that locally read endoscopies will be used for Mayo Score assessments at week 52 and week 104/ET.
- Removed specification that hepatitis B DNA virus test details are not required for subjects with only hepatitis B surface antigen (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 section.
- Updated the number of subjects.

EU CTR alignment

- Included Country Specific Supplements for France, Italy, and Germany to the appendix section.

Key administrative changes

- Added the NCT number and EU CT number in the title page of the protocol.
- Made typographical, formatting, numbering, and abbreviation changes throughout the protocol.

Approval Signatures

Document Name: Protocol Amendment efavaleukin alfa 20210210 2

Document Description: Protocol efavaleukin alfa 20210210 Amendment 2

Document Number: CLIN-000287361

Approval Date: 19 Jul 2024

Type of Study Protocol: Amendment

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