lStatistical Analysis Plan

Protocol Title:	A Phase 2, Dose-finding, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of Efavaleukin Alfa Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis
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Version Number	Date	Summary of Changes, including rationale for changes
Original (v1.0)	01FEB2022	Not Applicable
Amendment 1 (v2.0)	28SEP2022	Updates to be consistent with protocol superseded amendment 2: • Renamed mucosal healing secondary and exploratory endpoints to combined endoscopic and histologic remission • Added Change from baseline in partial Mayo score at each assessment through week 12 for the phase 2 Induction period exploratory endpoint. • Updated Corticosteroid-free clinical remission at week 52 endpoint to be for subjects receiving corticosteroids at randomization, original endpoint was for subjects receiving corticosteroid at week 12 • Replaced rectosigmoidoscopy with endoscopy throughout • Updated study design language in regards to ending IP, early termination visit, safety follow up visit, and entry into the long term extension study. • Updated DMC meeting frequency • Updated language for disease worsening criteria during long term treatment period [redacted] • Updated Full Analysis Set to include all randomized subjects Other updates: • Updated the definition for actual treatment group in the overall study period to be a combination of the actual treatment group in the induction period and actual treatment group in the long term treatment period • Added ‘study day 90’ in definition of Induction Adverse event exposure period and end of induction date. • Updated definition for exposure adjusted adverse event analysis to include all events up to EOS • Updated baseline definition for fecal calprotectin

		• Updated the method of analysis for subject accountability to summarize the induction period and overall study period separately • Added medical history and procedures to the imputation rules in Appendix **C** • Added Overall summary of subject incidence of treatment-emergent adverse events and by preferred term and worst severity grade will be provided by anti-AMG592 and Anti-IL-2 antibody status.
Amendment 2 (v3.0)	**19FEB2025**	**Updates to be consistent with protocol amendment 3, 4 and decision of IA3 to terminate the study:** • **Sample size reduced to 240 from 320** • **Clarified definition of intercurrent events** • **Added definitions for Endoscopic Remission, Clinical Remission and Clinical Response based on local endoscopy score** • **Added Appendix D: Mayo Score Categories** • **Select exploratory endpoints removed** • **Covariate and subgroup analyses removed** • **Other administrative updates**

Table of Contents

List of Tables

List of Abbreviations

Abbreviation	Explanation
ANCOVA	Analysis of Covariance
ASA	Aminosalicylates
COVID-19	Coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DAP	Data Access Plan
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GSO-DM	Global Study Operations-Data Management
hsCRP	High Sensitivity C-reactive Protein
IBG	Independent Biostatistics Group
IL-2	Interleukin-2
IRT	Interactive Response Technology
IV	Intravaneous(ly)
JAK	Janus kinase
NCT	National Clinical Trials
PGA	Physician's Global Assessment
PRO	Patient Reported Outcome
[redacted]	
QTc interval	QT interval corrected for heart rate using accepted methodology
[redacted]	
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol **superseded** amendments **3 and 4** for study 20170104, Efavaleukin Alfa dated **21 August 2024.** The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	**Endpoints**
Primary	
• To evaluate the effect of efavaleukin alfa on induction of clinical remission	• Clinical remission at week 12
Primary Estimand	
Variable: Clinical remission at week 12 Estimator: Difference in clinical remission rates Population: All subjects with moderately to severely active UC with inadequate response, loss of response, or intolerance to at least 1 of the following: conventional therapy, biologics, or targeted small molecules, who are randomized and received at least 1 dose of investigational product. Treatments: Each efavaleukin alfa dose group and placebo. Intercurrent event – composite variable strategy: **Subjects will be considered as not meeting the endpoint if:** i. **They initiate or increase the dose of UC related protocol-prohibited medication or concomitant UC medication between the date of the screening endoscopy and the week 12 endoscopy.** **ii.** Discontinuation of investigational product **on or prior to the end of induction period.** **iii. A colectomy (partial or total) or an ostomy.**	
Secondary	
• To evaluate the effect of efavaleukin alfa on induction of clinical response	• Clinical response at week 12
• To evaluate the effect of efavaleukin alfa on induction of endoscopic remission	• Endoscopic remission at week 12

• To evaluate the effect of efavaleukin alfa on induction of symptomatic remission	• Symptomatic remission at week 12
• To evaluate the effect of efavaleukin alfa as induction therapy on combined endoscopic and histologic remission	• Combined endoscopic remission and histologic remission of the colon tissue at week 12
• To evaluate the effect of efavaleukin alfa as induction therapy on change in histological score	• Change from baseline in histological score at week 12 as measured by Geboes score
• To evaluate the safety and tolerability of efavaleukin alfa	• Treatment-emergent adverse events

UC = ulcerative colitis

Phase 2 Induction Period

Exploratory	
• To explore the effect of efavaleukin alfa as induction therapy on calprotectin levels in fecal samples	• Change from baseline in fecal calprotectin at week 12
• To explore efavaleukin alfa immunogenicity	• Anti-efavaleukin alfa antibodies and crossreactivity with IL-2 • Anti-efavaleukin alfa and anti-IL-2 neutralizing antibodies

IL-2 = interleukin-2.

Long-term Treatment Period

Exploratory	
• To explore efavaleukin alfa immunogenicity during long-term treatment	• Anti-efavaleukin alfa antibodies and crossreactivity with IL-2 • Anti-efavaleukin alfa and anti-IL-2 neutralizing antibodies

IL-2 = interleukin-2.

2.2 Hypotheses and/or Estimations

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

3. Study Overview

3.1 Study Design

This phase 2 dose-finding study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week induction study of efavaleukin alfa in subjects with moderately to severely active UC who have failed at least 1 of the following: conventional therapy (eg, immunomodulators, corticosteroids), biologic therapy, or targeted small molecule. This study will be used to establish the efavaleukin alfa induction dose and maintenance dose/dosing regimens for continued development. Subjects who complete the 12-week induction period will have the option to be treated in an exploratory long-term treatment period for up to 40 additional weeks if in the opinion of the investigator they may benefit from continued treatment. The primary analysis will occur after all subjects have had the opportunity to complete the week 12 visit. All primary and secondary objectives will be evaluated at the primary analysis.

Induction Period

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

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

Randomization will be stratified by prior experience with at least 1 biologic or targeted small molecule (yes/no) and corticosteroid use at randomization (yes/no). A maximum of 30% of enrolled subjects are allowed to be naïve to biologic or targeted small molecule therapy.

Clinical remission and clinical response will be assessed at the end of the 12-week induction period by the modified Mayo score using centrally read endoscopy subscore

Interim analyses will be performed to assess futility.

An independent Data Monitoring Committee (DMC) will oversee safety and overall conduct of the study. The first 2 DMC meetings will occur after the first 20 subjects randomized have had the opportunity to complete the [redacted] and week 12 visits. Thereafter the DMC will plan to meet approximately every 3 months until Amgen is unblinded at the primary analysis. After Amgen is unblinded, the DMC will plan to meet

every 6 months. Ad hoc meetings can be scheduled as needed. The DMC will also review all available safety and efficacy data for interim analyses.

Long-term Treatment Period

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

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

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

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

Efficacy evaluations during the long-term treatment period will include the total and partial Mayo score, fecal calprotectin, and corticosteroid use. The modified Mayo score

(including endoscopy) and mucosal biopsies for histopathology will be assessed at week 52/early termination visit.

If a subject discontinues investigational product prior to week 52, the subject will be encouraged to maintain the planned scheduled assessments through week 52. If the subject discontinues the study completely prior to week 52, the subject should complete an early termination (ET) visit (ie, week 52 visit procedures) which must be scheduled to allow for [redacted] who complete the week 52 endoscopy and who, in the opinion of the investigator, may benefit from continued treatment, will be assessed for eligibility to roll over into the Phase 2 Long Term Extension Study (20210210).

[redacted]

3.2 Sample Size

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

[redacted]

3.3 Adaptive Design

Interim analyses will be conducted to assess for futility. [redacted]. Futility will be assessed at each interim. (Section 7.1).

The interim analyses will be conducted by an external Independent Biostatistics Group (IBG) and results evaluated by an independent DMC. In the case where pre specified decision rules are met at a planned interim analysis, a Data Access Plan (DAP) Team will be invoked. The DAP Team is comprised of a small team of senior members internal to Amgen but external to the study team. To facilitate final decision making, the DAP Team may evaluate unblinded results. Further details will be described in a Data Access Plan.

The study team, investigators and subjects will remain blinded to the results of the IAs unless the DAP team have made the decision to terminate the trial.

4. Covariates and Subgroups

4.1 Planned Covariates

The analysis of the primary endpoint will include randomization stratification factors [prior experience with at least 1 biologic or targeted small molecule (Yes/No), corticosteroid use at randomization (Yes/No)] from the interactive response technology (IRT) system as main covariates in the model.

4.2 Subgroups

No subgroup analysis is planned for the final analysis of the study.

5. Definitions

5.1 Basic Definition

Investigational Product (IP):

The term investigational product is used in reference to efavaleukin alfa and placebo.

Enrollment/Randomization Date:

The enrollment/randomization date is the date on which a subject is assigned to a treatment group at the start of the induction period by the IRT system.

First Dose Date:

The first dose date is the date of administration of the first dose of IP; this may or may not be the same as randomization date.

Placebo Nonresponder:

A subject randomized to placebo who has not achieved clinical response by week 12.

Placebo Responder:

A subject randomized to placebo who achieves clinical response at week 12.

Actual Treatment Received in the Induction Period:

The actual treatment received in the induction period is the IP the subject actually received up to the end of induction date, regardless of what the subject was randomized to. In cases where a subject received both efavaleukin alfa and placebo, the actual treatment received will be the efavaleukin alfa dose. In cases where a subject received multiple efavaleukin alfa doses, the actual treatment received will be based on the maximum of efavaleukin alfa doses received. **In cases where a subject received an efavaleukin alfa dose higher than the highest dose specified in the protocol, the actual treatment received will be the highest dose.**

Actual Treatment Received in the Long Term Treatment Period:

The actual treatment received in the long term treatment period is the IP the subject received from week 12 until EOS, regardless of treatment assigned by IRT. In cases where a subject received both efavaleukin alfa and placebo, the actual treatment received will be the efavaleukin alfa dose. In cases where a subject received multiple efavaleukin alfa doses, the actual treatment received will be based on the maximum of efavaleukin alfa doses received. **In cases where a subject received an efavaleukin alfa dose higher than the highest dose specified in the protocol, the actual treatment received will be the highest dose.**

Actual Treatment Group in the Overall Study Period

The actual treatment group in the overall study period is a combination of the actual treatment received in the induction period plus the actual treatment received in the long term treatment period (eg, placebo [redacted] overall, AMG 592 [redacted]ug [redacted]overall, AMG 592 [redacted]ug [redacted] overall, AMG 592 [redacted]ug [redacted] overall, placebo [redacted]induction/AMG 592 [redacted]ug [redacted] long term treatment).

Duration of Induction Period IP Exposure:

The duration of induction period IP exposure will be derived as the last date of IP administration prior to the week 12 endoscopy (or prior to EOS for subjects who do not have a week 12 endoscopy) plus 13 days (14 day window - 1), the day of first IP administration after the week 12 endoscopy - 1**,** EOS, or data cutoff date, whichever occurs first, minus the day of first IP administration + 1 day.

Duration of IP Exposure (Overall Study):

The duration of IP exposure (overall study) will be derived as the last date of IP administration prior to EOS plus 13 days (14 day window - 1)**,** EOS, or data cutoff date, whichever occurs first, minus the day of first IP administration + 1 day.

Duration of Efavaleukin Alfa Exposure:

The duration of efavaleukin alfa exposure will be derived as the date of the last administration of efavaleukin alfa plus 13 days (14 day window - 1), EOS, or data cutoff date, whichever occurs first, minus the date of first efavaleukin alfa administration + 1 day.

Duration of Long-term Treatment Period IP Exposure:

The duration of long-term treatment period IP exposure for subjects who receive at least one dose of IP in the long-term treatment period will be derived as the last date of IP administration plus 13 days (14 day window - 1), EOS, or data cutoff date, whichever occurs first, minus the day of first IP administration after the [redacted] endoscopy +1 day.

Completion of IP in the induction period:

A subject will be considered as completing IP in the induction period if they do not discontinue IP prior to the **end of the induction period**. A subject will be considered as completing IP in the long-term treatment period if the End of IP reason is “Completed” on the End of IP eCRF.

Treatment-emergent adverse event (TEAE):

Treatment-emergent adverse events are events categorized as Adverse Events (AEs) starting on or after first dose of IP as determined by “Did event start before first dose of investigational product?” equal to “No” or missing on the Events eCRF and up to the EOS date.

Treatment-related Adverse Event (TRAE):

A treatment-related AE is any treatment-emergent AE with the relationship flag on the Events eCRF indicating there is a reasonable possibility that the event may have been caused by investigational medicinal product as determined by the investigator. In the unlikely event that the relationship is missing, the treatment-emergent event will be considered treatment-related and documented in a footnote of the treatment-related summary**.**

Induction Adverse Event Exposure Period:

Induction adverse event exposure period starts on the date of the first dose of IP up to min[EOS date, study day 90, max(week 12 IP date - 1, week 12 endoscopy date)].

Exposure-Adjusted Adverse Events:

The exposure for the analysis of exposure adjusted TEAEs and serious TEAEs for the overall study period is defined for each subject as **(EOS – first dose date +1)**.

Baseline medication:

Baseline medication is defined as any medication with start date on or before study day 1 and ongoing while on study.

Concomitant medication:

Concomitant medication is defined as any medication with start date prior to study day 1 and ongoing while on study or any medication with start date on or after study day 1 and up to the EOS.

Prior medication:

Prior medication is defined as any medication with an end date prior to study day 1.

UC related protocol-prohibited medications:

Following medications will be classified as UC related protocol-prohibited medications:

Drug Class	Medication Restrictions
Anti-TNF antibodies (eg, infliximab, adalimumab, golimumab)	**Discontinue at least 8 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently**
Anti-integrin antibodies (eg, vedolizumab)	**Discontinue at least 8 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently**
IL-12/23 antagonist (eg, ustekinumab)	**Discontinue at least 8 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently**

JAK inhibitors (eg, tofacitinib)	**Discontinue at least 4 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently**
S1P modulators (eg, ozanimod)	**Discontinue at least 4 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently**
Any other commercially approved biologic agent or targeted small molecule	**Discontinue at least 8 weeks prior to screening endoscopy or 5 half-lives prior to screening endoscopy, whichever is longer, and prohibited unless the subject has stopped investigational product permanently**
Immunomodulatory medications oral cyclosporine, intravenous cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, or thalidomide	**Discontinue at least 4 weeks prior to screening endoscopy and prohibited throughout duration of study**
Any investigational biologic therapy	**Discontinue at least 8 weeks prior to screening endoscopy or 5 half-lives prior to screening endoscopy, whichever is longer, and prohibited throughout duration of study**
Apheresis (eg, Adacolumn® apheresis)	**Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study**
T cell depleting agents (eg, antithymocyte globulin, Campath).	**Patients with exposure within 12 months prior to screening not eligible to be enrolled.**
Recombinant IL-2 (eg, Proleukin®).	**Patients with any previous exposure not eligible to be enrolled.**
Corticosteroid enemas, corticosteroid suppositories, a course of IV	**Discontinue at least 2 weeks prior to screening endoscopy and prohibited**

corticosteroids or intramuscular corticosteroids, or oral budesonide standard formulation (not oral budesonide MMX)	**unless the subject has stopped investigational product permanently**
5-ASA enemas or 5-ASA suppositories	**Discontinue at least 2 weeks prior to screening endoscopy and prohibited unless the subject has stopped investigational product permanently**
Live vaccines	**Last vaccination (if any) given at least 5 weeks prior to screening. Live vaccines are prohibited throughout the treatment period and for up to 6 weeks after the last dose of investigational product in the study.**
Any other investigational therapies or device	**Prohibited throughout duration of study.**
Abbreviations: 5-ASA = 5-aminosalicyclic acid; IL-2 = interleukin-2; IL-12/23 = interleukin 12/23; IV = intravenous; JAK = Janus Kinase; TNF = tumor necrosis factor; UC = ulcerative colitis.	

Concomitant UC medication:

Following medications will be classified as concomitant UC medication:

- **Oral 5-ASA**
- **Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate)**
- **Oral corticosteroids**

Biologic Therapy Classes:

Biologic therapy classes include:

- Anti-TNF agents: **Infliximab, Adalimumab, Golimumab**
- Integrin receptor antagonists: **Vedolizumab**
- Interleukin inhibitors: **Ustekinumab (an anti-interleukin-12/23 antibody), Mirikizumab (a monoclonal antibody that targets the p19 subunit of interleukin-23), Risankizumab (a monoclonal antibody directed against the p19 subunit of IL-23)**

Targeted Small Molecules:

Targeted small molecules include:

- **Janus kinase (JAK) inhibitors: Tofacitinib and Upadacitinib**
- **Sphingosine-1-phosphate (S1P) receptor modulators: Ozanimod and Etrasimod**

5.2 Study Points of Reference

Baseline:

Baseline fecal calprotectin is the last measurement taken on or before the date of the first dose of IP.

Baseline for all other parameters is the last measurement for the endpoint of interest taken before the first dose of IP. If the measurement is taken on the same day as the first dose and the exact measurement time relative to the first dose is unknown, it will be assumed to have been taken prior to the first dose of IP.

If a subject did not receive IP, baseline is the closest recorded measurement on or prior to the randomization date for all parameters.

Study Day 1:

Study day 1 for each subject is the first day of IP administration or the day of randomization for subjects who did not receive IP.

Study Day:

Study day for each subject is defined as (day of interest - study day 1) + 1 for dates on or after study day 1, or (day of interest - study day 1) for dates prior to study day 1.

5.3 Study Dates

End of Induction Date:

End of Induction date for each subject is defined as date of the week 12 endoscopy. For subjects who discontinued from the study before completing the week 12 visit, or did not have a week 12 endoscopy, the end of induction date will be min(Study Day 90, EOS).

Start of Long-Term Follow-Up treatment period:

For subjects who continue into the long-term follow-up period, the start date is defined as the end of induction date plus one day.

End of Study Date:

EOS for each subject is the date recorded on the EOS **e**CRF page.

5.4 Arithmetic Calculations

Change from Baseline:

The arithmetic difference between a post-baseline value and baseline for a given timepoint:

(post-baseline value – baseline value).

Percent Change from Baseline:

The change from baseline divided by baseline value and multiplied by 100:

(change from baseline / baseline) * 100.

If baseline is zero, the percent change from baseline will be set to zero.

Fold Change from Baseline:

Fold change from baseline equals the post-baseline value divided by the baseline value**.** If the change from baseline is not equal to 0 and the baseline value is 0 then fold change is not defined. If the change from baseline is equal to 0 and the baseline value is also 0 then fold change is 1.

5.5 Definition of Study Endpoints

Individual Mayo Subscore:

There are 4 Individual Mayo subscores; stool frequency, rectal bleeding, centrally read endoscopy findings, and physician's global assessment (PGA), with each subscore graded semi-quantitatively on a score of 0 to 3.

Further explanation given in Appendix D for the full definition of Mayo subscores and calculation.

Total Mayo Score:

The total Mayo score is a composite index of the sum of the individual Mayo subscores, with each item graded semi-quantitatively on a score of 0 to 3, for a maximal total score of 12. The total Mayo score ranges from 0 to 12 points.

Modified Mayo Score:

The modified Mayo score is the total Mayo score without the physician's global assessment subscore and ranges from 0 to 9 points.

Partial Mayo Score:

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

Clinical Remission:

Clinical remission is defined as modified Mayo score 0 to 2 including rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and a centrally read endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

Clinical Remission (Using Local Endoscopy Score):

Clinical remission is defined as modified Mayo score (based on local endoscopy score) 0 to 2 including rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and a locally read endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

Clinical Response:

Clinical response is defined as 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.

Clinical Response (Using Local Endoscopy Score):

Clinical response is defined as a decrease from baseline in the modified Mayo score (based on local endoscopy 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.

Endoscopic Remission:

Endoscopic remission is defined as Mayo centrally read endoscopy subscore of 0 or 1 (modified so that a score of 1 does not include friability).

Endoscopic Remission (Using Local Endoscopy Score):

Endoscopic remission is defined as Mayo locally read endoscopy subscore of 0 or 1 (modified so that a score of 1 does not include friability).

Symptomatic Remission:

Symptomatic remission is defined as Mayo stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0.

Combined endoscopic and histologic remission:

Combined endoscopic and histologic remission is defined as combined endoscopic remission (Mayo centrally read 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 [Geboes, 2000]).

Rectal Bleeding and Stool Frequency Subscores:

Rectal bleeding and number of stools per day will be recorded in the Mayo Daily Symptom Diary by the patient. The stool frequency subscore will be calculated based on the number of stools per day more than the reference number of stools. The reference number of stools is defined as the number of stools in a 24-hour period when in remission from UC prior to enrollment into the study. If the subject has never achieved remission, the number of stools per day before initial onset of signs and symptoms of UC will be used.

The subscores will be derived from the most recent 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.

Rules for consideration of visit dates are defined in Appendix E.

UC Complications:

UC complications are defined as adverse events which have been categorized as related to UC on the Events eCRF.

Worst Case Imputation:

Worst case imputation will be used for missing postbaseline values for Geboes score, total Mayo score, partial Mayo score, and individual Mayo subscores. **In other words,** missing postbaseline values at any visit will be imputed using the highest score observed across baseline and all postbaseline visits.

6. Analysis Sets

6.1 Full Analysis Set (FAS)

All subjects randomized. Data will be analyzed based on randomized induction period treatment group. **Subject data from site 66164 are not included in the analysis set because the site closed due to noncompliance with the protocol and FDA regulations.**

6.2 Safety Analysis Set

Subjects randomized and received at least 1 dose of investigational product. Data will be analyzed according to actual treatment received. **Subject data from site 66164 are not included in the analysis set because the site closed due to noncompliance with the protocol and FDA regulations.**

6.3 Interim Analysis Sets

The interim analysis sets will include all subjects enrolled and had the opportunity to complete the week 12 visit by the data cutoff date for the respective interim analysis.

6.4 Long-term Treatment Period Efficacy Analysis Set

The long-term treatment period efficacy analysis set is defined as all subjects who received at least one dose of any efavaleukin alfa dose in the induction period plus subjects who were randomized to placebo in the induction period and received at least one dose of IP in the long-term treatment period. Data will be analyzed according to randomized treatment in the induction period. The exception will be subjects randomized to placebo in the induction period who will be further categorized into the treatment assigned via IRT in the long-term treatment period (i.e. assigned placebo in long-term treatment period and assigned efavaleukin alfa in long-term treatment period). **Subject**

data from site 66164 are not included in the analysis set because the site closed due to noncompliance with the protocol and FDA regulations.

6.5 Anti-drug Antibody Analysis Set

Anti-drug Antibody Analysis Set is defined as the subset of subjects in the Safety Analysis Set who had at least 1 evaluable anti-drug antibody test. Immunogenicity data will be analyzed according to the actual treatment received. **Subject data from site 66164 are not included in the analysis set because the site closed due to noncompliance with the protocol and FDA regulations.**

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Interim analyses will be conducted to assess for futility. Interim analyses will be conducted by an external Independent Biostatistics Group and results evaluated by an independent DMC.

where $d \in \{$ μg , μg , μg $\}$.

In the case where prespecified decision rules are met at a planned interim analysis, a Data Access Plan (DAP) Team will be invoked. The DAP Team is comprised of a small team of senior executives internal to Amgen but external to the study team. To facilitate

final decision making, the DAP Team may evaluate unblinded results. Further details will be described in a Data Access Plan.

The study team, investigators, and subjects will remain blinded to the results of the interim analyses.

7.2 Primary Analysis

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

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

7.3 Final Analysis

Final analysis activities will commence upon achieving the EOS, defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (i.e. Last subject last visit), including safety follow-up. The final analysis will include analysis of efficacy and safety data collected during the exploratory long-term treatment period.

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

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database. All laboratory values from the central laboratory will be transferred to GSO-DM. All Patient Reported Outcome (PRO) data, endoscopy results (including Mayo endoscopic subscore and Geboes score from the mucosal biopsy), and individual Mayo

subscores from the central vendors will be transferred to GSO-DM. All other data will be captured on the eCRF.

8.3 Handling of Missing and Incomplete Data

Subjects may have missing specific data points for a variety of reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of a specific clinical measurement at its planned clinical visit. Missing data will not be imputed, except for the data points described below.

Non-responder imputation will be used to impute missing data for the following binary endpoints: clinical remission, clinical response, endoscopic remission, symptomatic remission, combined endoscopic and histologic remission, corticosteroid-free clinical remission.

If a subject has missing data for any of these endpoints, (including missing one or more subscores contributing to the endpoint) at any scheduled visit, the subject will be considered as not meeting the endpoint for that specific visit.

Missing data for the following continuous endpoints will be imputed with worst case imputation: change in Geboes score, total Mayo score, partial Mayo score, and individual Mayo subscores.

Observed subscores will be used in the calculation of total and partial mayo score, where available. If one or more individual subscores is missing at a given post-baseline timepoint, the missing subscore will be imputed using the worst (highest) observed score across all available baseline and post-baseline visits up to week 12. The total/partial mayo score will be calculated using the imputed subscores, along with observed subscores, if available for that visit.

Laboratory measurements that are below the lower quantification limits will be considered equal to the lower limit of quantification for all analyses unless explicitly noted otherwise.

Incomplete UC diagnosis date will be imputed as follows:

- If day is missing but month and year are present, impute to the last day of the month
- If day and month are missing and year is present, impute to the 31st December of that year

Missing and incomplete dates of medical history, procedures, AE, concomitant medication and hospitalization dates will be imputed as outlined in Appendix C.

8.4 Detection of Bias

Important protocol deviations and early withdrawal from treatment and from study may bias the results of the study. The incidence of these factors will be assessed and reason for early withdrawals will be tabulated.

8.5 Outliers

Scatter plots will be examined to identify potential outliers in any of the continuous variables and frequencies of the categorical data will be examined to identify questionable values. The validity of any questionable values will be verified, and observations found to be due to data entry errors will be queried. Potential outliers that are not due to data entry error will be included in the analysis.

8.6 Distributional Characteristics

Not applicable for this study.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

All categorical variables will be summarized using the number and percent of subjects falling into each category and all continuous variables will be summarized using mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, maximum, and number of subjects with observations.

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

Safety endpoints will be summarized descriptively, including treatment-emergent adverse events and serious adverse events in the induction period, clinically significant changes in laboratory values and vital signs, and incidence of antidrug antibodies.

Exposure-adjusted treatment-emergent adverse events and serious adverse events will be summarized for the overall study period.

9.2 Subject Accountability

The number and percent of subjects who were randomized, received investigational product in the induction period, discontinued investigational product in the induction period (including reasons for discontinuing), completed investigational product in the induction period, and completed the induction period will be summarized overall and by randomized treatment group.

The number and percent of subjects who completed investigational product for the overall study, discontinued investigational product at any time during the study (including reasons for discontinuing), and overall study completion (defined as completed study on the eCRF) will be summarized overall, by randomized treatment group, and week 12 response status (subjects randomized to placebo only).

Summary of subjects who discontinue investigational product/study due to COVID-19 control measures will be included.

Key study dates for the first subject enrolled, last subject enrolled, last subject's end of investigational product, and last subject's EOS will be presented.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject’s initial visit and updated during the IPD reviews throughout the study prior to final database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

The final IPD list will be used to produce the summary of IPDs table and the list of subjects with IPDs.

IPDs related to COVID-19 control measures will be summarized separately.

9.4 Demographic and Baseline Characteristics

The following demographic, baseline characteristics, baseline disease characteristics and baseline and prior medications of interest will be summarized descriptively by randomized treatment group.

Demographics:

- Age (years)
- Age groups (≥ 18 to < 50, ≥ 50 and 18 – 64, 65 – 74,75 – 84)
- Sex (male, female)
- Race (American Indian or Alaska, Native Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Geographic region (Eastern Europe, Asia Pacific, Rest of World)

Baseline Characteristics:

- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)

Baseline Disease Characteristics:

- Modified Mayo score at baseline
- Total Mayo score at baseline
- Individual Mayo subscores at baseline
- **Partial Mayo score**
- Disease localization (proctosigmoiditis, left-sided colitis, extensive colitis, pancolitis)
- Duration of UC (years from date of diagnosis to first dose date)
- Fecal calprotectin

Baseline medications:

- Oral 5-aminosalicylates (5-ASA)
- Corticosteroid
- Immunomodulator (azathioprine, 6-mercaptopurine, methotrexate)

Prior medication history:

- Prior experience, including reason for stopping, for the following medication classes:
  - conventional therapies (azathioprine, 6-mercaptopurine, methotrexate, corticosteroids)

- biologic therapy (including number of prior biologic therapy classes and total number of prior biologics)
- anti-TNF therapy
- targeted small molecule therapy (ie. Janus kinase [JAK] inhibitor)

9.5 Efficacy Analyses

The efficacy analyses are summarized in Table 9-1, Table 9-2, Table 9-3 and Table 9-4 and analyses of efficacy endpoints are described from Section 9.5.1 to Section 9.5.4.

Table 9-1. Primary Efficacy Estimand Summary Table

Endpoint	Primary Summary and Analysis Method - FAS	Additional Analysis
Clinical remission at week 12	Logistic regression model described in 9.5.1.1 **Composite variable intercurrent event strategy**	Treatment policy intercurrent event strategy

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method - FAS
Clinical response at week 12 Endoscopic remission at week 12 Symptomatic remission at week 12 Combined endoscopic remission and histologic remission of the colon tissue at week 12	Logistic regression model described in 9.5.1.1 **Composite variable intercurrent event strategy**
Change from baseline in histological score at week 12 as measured by Geboes score	ANCOVA model described in 9.5.1.2 **Composite variable intercurrent event strategy**

Table 9-3. Phase 2 Induction Period Exploratory Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method - FAS
Change from baseline in fecal calprotectin at week 12	Repeated measures model described in 9.5.1.3 **Composite variable intercurrent event strategy**

9.5.1 Descriptions of Statistical Models

9.5.1.1 Logistic Regression Model

The logistic regression model will be used to test the difference in rates between each efavaleukin alfa dose and placebo (Ge et al, 2011). The stratification factors as captured in IRT will be included as covariates.

The estimate of the risk difference between each efavaleukin alfa dose and placebo, the corresponding 2-sided 95% Wald confidence interval, and the p-value obtained from the logistic regression model will be provided.

In case the logistic regression model does not converge due to separation, Firth's modified logistic regression may be used to reduce bias in the parameter estimates [Heinze and Schemper (2002)].

9.5.1.2 ANCOVA Model

Analysis of covariance (ANCOVA) model will be used to test the difference between each efavaleukin alfa dose and placebo, with stratification factors as captured in IRT as covariates. The least-squares mean estimate of the treatment differences (efavaleukin alfa dose group – placebo) and the corresponding 95% confidence intervals will be summarized.

9.5.1.3 Repeated Measures Model

The repeated measures model will be used to test the difference between each efavaleukin alfa dose and placebo at each scheduled visit. The model will include terms for treatment group, stratification factors (from IRT), scheduled visit, and the interaction of treatment with scheduled visit. The least-squares mean estimate of the treatment differences (efavaleukin alfa dose group – placebo) and the corresponding 95% confidence intervals will be summarized for each scheduled visit.

To account for repeated measurements within a subject across the visits, the model will use an unstructured covariance.

9.5.2 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

The primary analysis of the primary efficacy estimand will use the logistic regression model described in Section 9.5.1.1 based on the Full Analysis Set (FAS) described in Section 6.1 and the subjects with missing data will be imputed using nonresponder imputation.

A composite variable strategy will be used to handle intercurrent events for the primary estimand. Subjects will be considered as not meeting the endpoint if they meet any of the following criteria:

- Initiation of or **increase the dose of UC related** protocol-prohibited medication or concomitant UC medication **between the date of the screening endoscopy and the week 12 endoscopy**
- **UC related protocol-prohibited medications include:**
  - **Any investigational therapy for Ulcerative Colitis**

- **Biologic agents (eg, Vedolizumab, Ustekinumab, Infliximab, Adalimumab, Golimumab)**
- **T cell depleting agents (eg, Antithymocyte immunoglobulin, Campath [Alemtuzumab])**
- **Recombinant IL-2 (eg, Proleukin [aldesleukin])**
- **Jak Inhibitors (eg, Baricitinib, Tofacitinib, Upadacitinib)**

- **Other immunomodulatory agents (eg, S1P modulators [Fingolimod and siponimod], ciclosporine, Mycophenolic acid, tacrolimus, sirolimus)**
- **Corticosteroids via IV, intramuscular, or rectal route**
- **5-ASAs via rectal route**
- **Concomitant UC medication includes:**
  - **Oral 5-ASA**
  - **Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate)**
  - **Oral corticosteroids**
- Discontinuation of investigational product on or prior to the **end of the induction period**

To assess the impact of the composite variable strategy for the intercurrent events, an additional analysis will be performed using the treatment policy strategy. In this analysis the actual remission status at week 12 will be used, regardless of each intercurrent event. Subjects with missing week 12 remission status will be imputed using nonresponder imputation.

9.5.3 Analyses of Secondary Efficacy Endpoint(s)

The logistic regression model described in Section 9.5.1.1 will be used to test the difference in rates between each efavaleukin alfa dose and placebo for the following secondary endpoints:

- Clinical response at week 12
- Endoscopic remission at week 12
- Symptomatic remission at week 12
- Combined endoscopic and histologic remission of the colon tissue at week 12

Subjects with missing data will be imputed using nonresponder imputation. The same incurrent event composite variable strategy as used for the primary estimand will be used for these secondary endpoints.

Change from baseline in histological score at week 12 as measured by Geboes score will be analyzed using an analysis of covariance (ANCOVA) model described in Section 9.5.1.2. Subjects with missing week 12 Geboes score, or who experience any of the intercurrent events described in Section 9.5.2 will be imputed using worst case imputation.

9.5.4 Analyses of Exploratory Efficacy Endpoint(s)

9.5.4.1 Phase 2 Induction Period Analyses of Exploratory Efficacy Endpoint

The repeated measures model described in Section 9.5.1.3 will be used to assess the difference between each efavaleukin alfa dose and placebo at each scheduled visit through week 12 for the following exploratory endpoints:

- Change from baseline in fecal calprotectin at week 12

9.5.4.2 Long-Term Treatment Period Analyses of Exploratory Efficacy Endpoint

Analysis of the long-term treatment period exploratory efficacy endpoints will use the long-term treatment period efficacy analysis set. Summary statistics will be used to summarize all long-term treatment period exploratory endpoints.

The same intercurrent event composite variable strategy as used for the primary estimand will be used for these exploratory endpoints.

9.6 Safety Analyses

9.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **27**.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term. The severity of each adverse event will be graded using CTCAE criteria version 5.0 or later (Appendix A). Summaries of adverse events during the induction adverse event exposure period will be presented by actual treatment received in the induction period. Exposure-adjusted subject incidence rates for the overall study period will be presented by actual treatment received in the overall study.

Subject incidence of all TEAEs, serious TEAEs, TEAEs leading to discontinuation from investigational product, fatal TEAEs, treatment-related TEAEs, treatment-related serious TEAEs, treatment-related TEAEs leading to discontinuation from investigational product,

treatment-related fatal TEAEs, and TEAEs of interest that occur in the induction adverse event exposure period will be summarized.

Subject incidence of treatment-emergent adverse events identified by COVID-19 standardized MedDRA queries and serious adverse events occurring on or after the COVID-19 infection that occur in the induction adverse event exposure period will also be summarized.

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen Medical Queries) that occur in the induction adverse event exposure period will also be summarized according to their categories and preferred term. Events of interest could include but are not limited to Hypersensitivity, Tachyarrhythmias, Tachypnea, Hematopoietic Cytopenia, Drug Reaction with Eosinophilia, Leucocyte Changes, Infection and Infestation, Cytokine Release Syndrome, and Injection Site Reaction. Number of episodes and duration of treatment-emergent injection site reactions will be further summarized by treatment group.

In addition, summaries of TEAEs and serious TEAEs occurring in at least 5% of the subjects in any treatment arm and serious TEAEs occurring in at least 2% of the subjects in any treatment arm by preferred term that occur in the induction adverse event exposure period will be provided in descending order of frequency.

Summaries of TEAEs and serious TEAEs that occur in the induction adverse event exposure period will be tabulated by system organ class, preferred term, and grade. An overall summary of adverse events by toxicity grade will be provided.

Exposure-adjusted subject incidence rate of TEAEs, serious TEAEs, TEAEs leading to discontinuation from investigational product, fatal TEAEs, treatment-related TEAEs, treatment-related serious TEAEs, treatment-related TEAEs leading to discontinuation from investigational product, treatment-related fatal TEAEs, and TEAEs of interest will be presented for the overall study period.

Overall summary of subject incidence of TEAEs and by preferred term and worst severity grade will be provided by anti-AMG592 and Anti-IL-2 antibody status.

9.6.2 Laboratory Test Results

Change and percent change from baseline in select clinical laboratory test results will be summarized over time by each treatment group. In addition, shift tables, from baseline to the worst on-study laboratory toxicity based on the CTCAE version 5 or later will be presented.

Subject incidence of worst post-baseline of eosinophils counts and percentages by the laboratory normal range will be tabulated by treatment group.

9.6.3 Vital Signs

The actual value, change and percent change from baseline in vital signs will be summarized over time by treatment arm for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature.

9.6.4 Physical Measurements

The actual value, change and percent change from baseline in weight and BMI will be summarized by treatment arm and by scheduled visit.

9.6.5 Electrocardiogram

The ECG (Electrocardiogram) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc (corrected QT Interval) 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.

9.6.6 Antibody Formation

The incidence and percentage of subjects who develop anti- efavaleukin alfa antibodies and cross reactive anti-IL-2 antibodies (binding and if positive, neutralizing) will be summarized by treatment group. Furthermore, the incidence and percentage of subjects with treatment-boosted anti- efavaleukin alfa antibodies will also be summarized.

In addition, subjects with positive binding and neutralizing anti-efavaleukin alfa results will be listed individually with corresponding time points.

9.6.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to IP by treatment arm and by study period and overall. Summary statistics will be provided for the total number of doses administered, total dose received, and total duration of IP exposure by treatment arm and by study period and overall.

9.6.8 Exposure to Other Protocol-permitted Therapy

Protocol-permitted therapy includes oral 5-ASA compounds, immunomodulators, and oral corticosteroids.

Descriptive statistics of number and percentage of subjects with dose modifications, including steroid tapering of corticosteroids in the long-term treatment period, will be produced by treatment arm.

The number and percentage of subjects taking oral 5-ASA compounds, immunomodulators, and oral corticosteroids will be provided.

9.6.9 Exposure to Concomitant Medication

Not applicable

9.7 Other Analysis

Not applicable

9.7.1 Analyses of Clinical Outcome Assessments

Not applicable

9.7.2 Analyses of Health Economic Endpoints

Not applicable

10. Analyses of Biomarker endpoints

Not applicable

11. Changes From Protocol-specified Analyses

- **The third interim analysis conducted for the study in August 2024 revealed that the study met futility criteria, leading to its termination. As a result of this decision, select exploratory endpoints originally included in the Statistical Analysis Plan (SAP) are being removed. These endpoints will not be discarded entirely; instead, they will be documented in a Supplemental Statistical Analysis Plan (SSAP) and will not be documented in CSR.**
- **Subject data from site 66164 are not included in the analysis set because the site closed due to noncompliance with the protocol and FDA regulations. The following listings for the affected subjects will be generated separately:**
  - **Adverse Events**
  - **Concomitant Medications**
  - **Laboratory Data**

12. Literature Citations / References

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13. Appendices

Appendix A. Reference Values/Toxicity Grades

Assessment of severity for each adverse event and serious adverse event reported during the study 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

Appendix B. Analytical Windows

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, to allow for variations in scheduling, the following visit windows will be used to assign evaluations to a most appropriate nominal visit for analysis and summarization. Furthermore, there will be no gaps between visit windows in order to include as many data points as possible for summarization.

If more than one actual visit (including the unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit dates are at the same distance from the target day, the latest visit with non-missing data will be considered for analysis.

If more than one evaluation falls on the same date and time for laboratory results, then the value with the smallest accession number will be used.

Analysis visit windows for selected assessments are included in tables below. For remaining assessments, no visit window will be applied.

		Study Day Window		
Analysis Visit	**Target Day**	**Vital Signs**	**Chemistry, Hematology Urinalysis**	**Fecal Calprotectin, hsCRP**
6 to 24 hour Post Dose	1	1-2		
48 to 96 hour Post Dose	3	3 - 5		
[redacted]		6 - 19	2 - 22 (Chemistry and Hematology only)	
		20 - 26		
		27 - 35	23 - 42 (Chemistry and Hematology) 2 - 42 (Urinalysis)	2 - 42
		36 - 49		
		50 - 63	43 - 70	43 - 70
		64 - 77		

[redacted]	78 - end of induction date	71 - end of induction date	71 - end of induction date
	(end of induction date + 1) - 105		
	106 - 119	(end of induction date + 1) - 126	
	120 - 133		
	134 - 147	127 - 154	
	148 - 161		
	162 - 175	155-182	(end of induction date + 1) - 210 (Fecal Calprotectin only)
	176 - 189		
	190 - 203	183-210	
	204 - 217		
	218 - 231	211-238	
	232 - 245		
	246 - 259	239-266	211 - 308 (Fecal Calprotectin only)
	260 - 273		
	274 - 287		
	288 - 301		
	302 - 315		
	316 - 329		
	330 - 343		

[redacted]	344 - 357		
	358 - 378	267-378	309 - 378 (Fecal Calprotectin only)

		Study Day Window			
Analysis Visit	**Target Day**	**Anti-efavaleukin alfa antibody**	**Partial Mayo Score, Physician Global Assessment (PGA)**	**Lymphocyte subset**	**Weight, Modified Mayo Score, endoscopy and Geboes score**
[redacted]		2 - 22	2 - 19	2 - 19	
			20 - 26	20 - 26	
		23 - 42	27 - 35		
			36 - 49	27 - 49	
		43 - 70	50 - 63		
			64 - 77		
		71 - end of induction date	78 - end of induction date	50 - end of induction date	2 - end of induction date
			(end of induction date + 1) - 126		
			127 - 154		

[redacted]	(end of induction date + 1) - 210	155 - 182	(end of induction date + 1) - 210	
		183 - 210		
		211 - 238		
	211 - 308	239 - 266	211 - 308	
		267 - 294		
		295 - 322		
		323 - 350		
	309 - 378	351 - 378	309 - 378	(end of induction date + 1) - 378

Appendix C. Handling of Dates, Incomplete Dates and Missing Dates

Imputation Rules for Partial or Missing Start Dates for Medical History, Procedures, AE, Conmeds (except corticosteroid recorded ended due to steroid tapering), Hospitalization dates.

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1=Impute the date of first dose; 2=Impute the first of the month; 3=Impute January 1 of the year; 4=Impute January 1 of the stop year
Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.

Imputation Rules for Partial or Missing Stop Dates

Initial imputation

- If the month and year are present, impute the last day of that month.
- If only the year is present, impute December 31 of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

If the imputed stop date is before the start date, set stop date to missing.

If the imputed stop date is after the death date, impute as death date.

Imputation Rules for Partial or Missing Death Dates

If death year and month are available but day is missing:

- If yyyymm for the date last known to be alive equals yyyymm for death date, set death date to the day after the date last known to be alive.
- If yyyymm for the date last known to be alive is less than the yyyymm for death date, set death date to the first day of the death month.

- If yyyymm for the date last known to be alive is greater than yyyymm for death date, assume date last known to be alive is in error, set death date to the first day of the death month.

If month and day are missing and year of death is known:

- If yyyy for the date last known to be alive equals yyyy for death date, set death date to the day after last known to be alive date.
- If yyyy for the date last known to be alive is less than yyyy for death date, set death date to the first day of the death year.
- If yyyy for the date last known to be alive is greater than yyyy for death date, assume date last known to be alive is in error, set death date to the first day of the death year.

If a death date is totally missing:

Set death date to the day after the date last known to be alive. If the date last known to be alive is a partial date, set it to the first day of the month last known to be alive or first day of the year last known to be alive if month is also missing.

Appendix D. Mayo Score Categories

Stool Frequency Subscore	Score
Normal number of stools for subject	0
1 or 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 with 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
Mayo Score = Stool Frequency + Rectal bleeding+ Endoscopic Subscore + Physician's Global Assessment	

Note: The Mayo score range from 0 to 12, with higher score of indicating more severe disease. Modified Mayo score excluded Physician's Global Assessment and ranges from 0 to 9. Composite stool frequency and rectal bleeding score ranges from 0 to 6. The original description of the Mayo score included friability in the definition of an endoscopic subscore of 1. Consistent with current clinical practice and regulatory guidance, the study excluded friability from the definition of an endoscopic subscore of 1.

Stool frequency reports the number of stools in a 24-hour period, relative to the normal number of stools for that patient. The reference "normal" stool frequency for that patient will be recorded electronically at the screening visit. The Normal SF (stool frequency) refers to when the patient was in remission or, if the patient has never achieved remission, the reported stool frequency before initial onset of signs and symptoms of ulcerative colitis. Remission refers to a period of time since being diagnosed with ulcerative colitis wen the patient is not experiencing any signs or symptoms relating to ulcerative colitis. This period of time may last a few weeks or a few months or may even last several years. The patient will record this electronically as souse data in the tablet device at the screening study visit.

Appendix E. Visit Date Considerations

- If the visit includes an actual endoscopy performed, then use the bowel preparation date.

- If the visit includes an actual endoscopy performed, but not getting 3 records from the bowel preparation date then use PGA assessment date.

- If the visit does not include an actual endoscopy performed, then use the PGA assessment date.

- If the visit does not include an actual endoscopy performed, but not getting 3 records from the PGA assessment date then use target assessment date.

- If the visit does not include an actual endoscopy performed and PGA assessment are also missing, then use target assessment date.

- If all above scenarios fails, then use worst case imputation.

The target assessment date for that visit should be used per Appendix B .

For sites located in France, site number 25001, 25002, 25003, 25004, and 25005, if a subject has an Endoscopy date recorded with a missing Bowel preparation date, then Endoscopy date will be considered for the Bowel preparation date. Bowel prep date may be missing as listed French sites may perform enema on the same day as endoscopy date. No imputation will be performed if Bowel preparation date is present.